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Clinical Value of Plasma-Iron Turnover Rate in Diagnosis and Management of Polycythemia[1,2]

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INTRODUCTION

Three major types of polycythemia are encountered in clinical practice. These are polycythemia vera, secondary polycythemia and so-called relative polycythemia, or "stress" erythrocytosis. Accurate classification of the polycythemic patient is essential, since proper management depends on the variety of disorder present.

Polycythemia vera is characterized by an absolute increase in the erythrocytic mass. Splenomegaly, leukocytosis and thrombocytosis are often present at some stage of the disease. Arterial and venous thrombosis is frequent in untreated patients. Present concepts link this disease with myelogenous leukemia and myelofibrosis in the "myeloproliferative" disorders. Administration of radiophosphorus is often the treatment of choice.

Secondary polycythemia is usually a compensatory response to hypoxia in patients who have venous-arterial shunts or chronic pulmonary disease. The erythrocytic mass usually is increased in proportion to the degree of oxygen desaturation of arterial blood. Splenomegaly, leukocytosis and thrombocytosis do not occur. Treatment is directed toward the primary underlying disease.

These first two types of polycythemia are well known and adequately described. In contrast, relative polycythemia is either not mentioned or given only scant discussion. In our clinical experience, it is a relatively common disorder and deserves greater study than it has been given so far. Relative polycythemia is characterized by a chronic reduction in plasma volume with a normal total erythrocytic mass, resulting in an apparent increase in erythrocytes (1).

[1]Read at the Seventh Annual Meeting of the Society of Nuclear Medicine, Estes Park, Colorado, June 22 to 25, 1960.

[2]From the Mayo Clinic and Mayo Foundation, Rochester, Minnesota. †Section of Medicine; *Section of Biochemistry.

Although polycythemia vera may occur in either sex, relative polycythemia is almost exclusively limited to males. In a hospital practice, these pseudopolycythemic patients often are admitted because of complications of occlusive vascular disease. In outpatients, a diagnosis of anxiety tension state often is made, and this has led some observers to label the disorder as "stress" erythrocytosis (1,2). Splenomegaly, leukocytosis and thrombocytosis do not occur. Treatment directed to the apparent polycythemia is usually not necessary, and use of radiophosphorus is contraindicated.

Figure 1 illustrates the differences in blood volume in two hypothetic patients, one with absolute and one with relative polycythemia. The volume of packed cells (hematocrit) is 60 per cent in both of these hypothetic polycythemic patients but for different reasons. The patient with relative polycythemia has a normal erythrocytic volume but a low plasma volume, whereas the patient with polycythemia vera has a normal plasma volume but an increased erythrocytic volume.

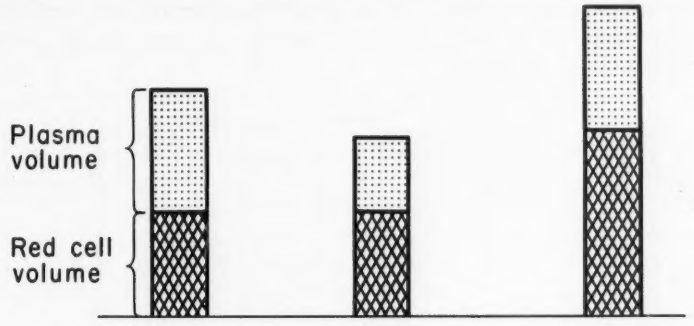
By utilizing these differential features, the clinician usually has little difficulty in arriving at the correct diagnosis. The major problem arises in distinguishing cases of mild early polycythemia vera without splenomegaly, leukocytosis or thrombocytosis from cases in which relative polycythemia is present. Ordinarily, determination of blood volume will settle the issue. However, some patients early in the course of polycythemia vera will have only a borderline increase in the erythrocytic volume associated with a low or low-normal plasma volume. In these instances, the differential diagnosis may be extremely difficult, and only the future course of the patient will settle the problem (3). The diagnosis of secondary polycythemia is usually not a major clinical problem and will not be considered further.

The production of erythrocytes by the bone marrow is normal in patients who have relative polycythemia, whereas it is increased in those with polycythemia vera (1,4). The plasma-iron turnover rate (PITR) has been shown to be a useful index of erythropoiesis; it has been reported to be uniformly increased in untreated patients with polycythemia vera but to be normal in patients who have relative polycythemia (4). The present study summarizes our experience with the practical clinical usefulness of the PITR in the diagnosis and management of polycythemia vera and relative polycythemia.

METHODS AND MATERIAL

The technic used for determining the PITR has been described in detail elsewhere (5). In brief, the plasma transferrin in an aliquot of the patient's whole blood is labeled in vitro with radioiron, and a portion then is returned to the patient by intravenous injection. Serial samples of blood are collected from the patient, and the plasma radioactivity is measured in a well type of scintillation counter. The resulting data, plotted on semilogarithmic paper, show an exponential decrease in radioactivity. The time for half of the initial radioactivity to disappear ($T\frac{1}{2}$) is determined from the disappearance slope. The plasma volume is determined by dividing the total count in the material injected by the count at time zero or, alternatively, by a dye technic. In some

patients with polycythemia vera, the plasma volume determined by the volume of distribution of radioiron ("iron space") was considerably greater than that determined by the dye method. Accordingly, the dye-determined plasma volume was used in calculating the PITR in most of the patients in this study. The concentration of serum iron was determined by a modification of Ramsay's method. (6)



	Normal	Relative polycythemia	Absolute polycythemia
Hematocrit	45	60	60
Plasma volume	3000	1800	3000
Red cell volume	2500	2500	4500
Total blood volume	5500	4300	7500

Fig. 1. Hypothetic partitions of blood volume in normal persons and in polycythemia. Hematocrit values are in percentage of packed cells; volumes are in milliliters.

The formula used for calculation of the PITR, expressed as milligrams per kilogram of body weight per day, is as follows:

$$\frac{0.693 \times \text{serum iron (mg/ml)} \times \text{plasma volume (ml)} \times 24}{\text{T½ (hr)} \times \text{patient's weight (kg)}}.$$

The erythrocytic volume was calculated from the plasma volume, using the hematocrit value corrected for trapped plasma (0.96) and for the central body hematocrit (0.91). The formula used was as follows:

$$\text{Erythrocytic volume} = \text{plasma volume} \times \frac{\text{hematocrit}}{\text{1-hematocrit}}.$$

Nineteen patients with polycythemia vera (15 in relapse and four in remission), 14 patients with relative polycythemia and six patients with polycythemia of an indeterminate type were studied.

The diagnosis of polycythemia vera or relative polycythemia was made by the hematologist without regard to the PITR. The normal erythrocytic

volume determined directly by use of radiochromium or radiophosphorus averages about 30 ml per kilogram (5). In our clinical practice, we hesitate to make an unequivocal diagnosis of polycythemia vera unless the inferred erythrocytic volume (calculated from the plasma volume and the corrected hematocrit as already noted) exceeds 43 ml per kilogram, or the patient has other supportive evidence of the disease, such as splenomegaly or thrombocytosis (3). Some of the patients with polycythemia vera in the present study had an erythrocytic volume less than this value because of previous treatment but were considered to be in relapse.

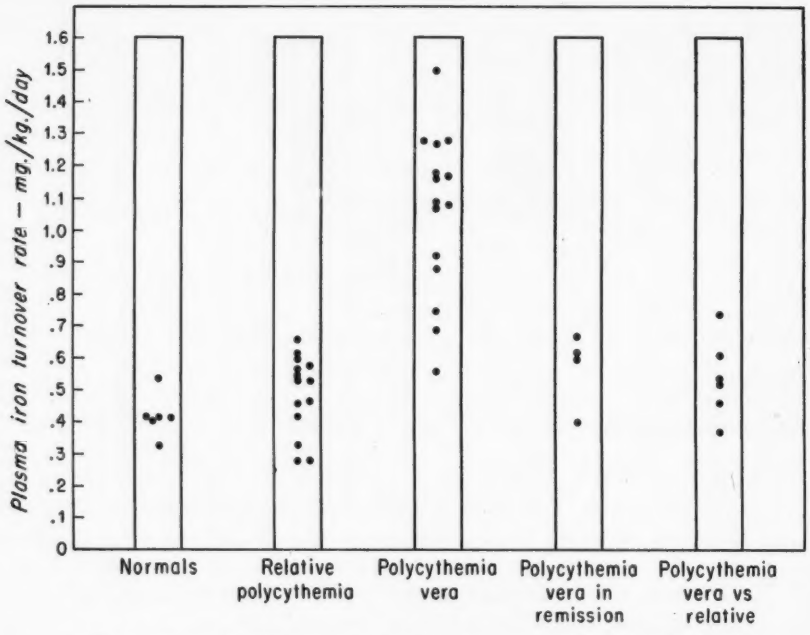


Fig. 2. Plasma-iron turnover rate in normal persons and in polycythemia.

RESULTS AND COMMENT

The complete data are given in Table 1 and the essential data are summarized in Table 2, which includes six controls. The PITR and the concentration of serum iron in the patients with relative polycythemia did not differ significantly from values in the controls. Statistical analysis showed a significant difference in the mean PITR and T½ between the patients with polycythemia vera and those who had relative polycythemia ($p<0.001$).

Although the mean T½ in the relative polycythemia group was shorter than that in the normals, the PITR remained in the normal range because the decreased plasma volume reduced the pool of plasma iron.

In the polycythemia vera group, the mean concentration of serum iron was considerably less than it was in the patients who had relative polycythemia (51 versus 111 micrograms per 100 ml), but the importance of this difference

TABLE 1.

CLINICAL, HEMATOLOGIC AND RADIOIRON DATA IN POLYCYTHEMIC PATIENTS

Case	Age, yr.	Sex	Weight, kg.	Hematocrit, per cent*	Serum iron, μg./100 ml.	$T_{½}$, minutes	Plasma volume, ml./kg.	PITR, mg./kg./day	Inferred red-cell volume, ml./kg.†
				Relative polycythemia					
1	29	M	91	54	103	62	34	0.57	30
2	63	M	95	58	93	90	29	0.28	29
3	76	M	82	52	97	80	38	0.46	31
4	37	M	97	56	155	85	34	0.62	33
5	52	M	97	54	119	118	32	0.33	28
6	44	M	88	61	117	63	28	0.53	32
7	53	M	73	60	64	37	34	0.60	38
8	33	M	78	57	118	95	35	0.47	35
9	54	M	91	58	173	96	30	0.53	30
10	69	M	80	57	67	37	31	0.55	31
11	64	M	76	61	175	85	28	0.58	33
12	27	M	117	55	73	80	31	0.28	29
13	58	M	78	54	83	68	35	0.42	31
14	35	M	95	57	122	62	36	0.66	36
Mean					111	76		0.48	
				Polycythemia vera in relapse					
15	73	M	70	55	58	25	40	0.92	37
16	67	M	85	63	49	18	47	1.27	57
17	58	M	69	55	135	49	43	1.18	40
18	58	M	63	74	128	45	45	1.28	84
19	71	F	72	53	13	14	45	0.56	52
20	57	M	70	59	36	21	42	0.69	44
21	68	F	72	67	55	15	35	1.28	48
22	49	M	75	62	36	19	62	1.17	73
23	62	F	45	63	23	10	65	1.50	79
24	59	M	72	63	38	16	45	1.07	55
25	70	M	69	66	34	17	54	1.09	72
26	75	F	44	59	21	11	59	1.16	61
27	46	F	54	54	43	25	44	0.75	39
28	47	F	69	63	54	15	30	1.08	35
29	48	F	64	66	37	18	43	0.88	57
Mean					51	21		1.06	

TABLE 1—Cont'd

Case	Age, yr.	Sex	Weight, kg.	Hematocrit, per cent*	Serum iron, μg./100 ml.	$T_{1/2}$, minutes	Plasma volume, ml./kg.	PITR, mg./kg./day	Inferred red-cell volume, ml./kg.†
Polycythemia vera in remission									
30	63	M	95	60	130	75	36	0.62	39
31	46	M	84	63	42	26	25	0.40	31
32	63	M	77	55	43	29	40	0.60	37
33	33	M	65	52	46	28	39	0.67	32
Mean					65	40		0.57	
Polycythemia, type indeterminate									
34	51	M	78	58	67	61	36	0.37	36
35	61	M	65	59	86	50	36	0.61	37
36	42	M	70	63	81	34	34	0.74	42
37	35	M	101	56	133	114	40	0.46	38
38	53	M	81	61	66	41	33	0.54	37
39	69	M	84	59	62	68	41	0.37	43
Mean					83	61		0.52	

*Uncorrected for trapped plasma.
†Calculated from plasma volume.

is questionable, since most of the former patients had undergone multiple phlebotomies in the past. Of interest is the fact that the only two patients in the polycythemia group with normal values for serum iron never had undergone phlebotomy.

The PITR of the patients who had relative polycythemia was separated cleanly from that in the polycythemia vera group except for three of the latter patients (Fig. 2). All three of these patients had extremely low concentrations of serum iron because of previous phlebotomies, so that, even though the $T_{1/2}$ was reduced in all of them, the PITR was not greatly increased.

Normal values for PITR in four patients with polycythemia vera who previously had been treated with radiophosphorus aided in the decision to withhold further treatment. Case 31 illustrates the value of the test. The patient in this instance had been treated with radiophosphorus 18 months previously and returned for consideration of further therapy. His hematocrit value was 63 per cent, but the PITR was well within normal limits. A repeat study of the blood volume showed a normal erythrocytic volume (31 ml per kilogram) but a great reduction in plasma volume, accounting for the increased hematocrit

value. The normal PITR gave additional confirmatory evidence of remission despite the increased percentage of packed cells.

Of particular interest is the group of six patients who could not be classified definitely on the basis of the available clinical evidence. Four of them had a normal PITR and low or low-normal values for plasma volume and probably are patients with relative polycythemia. The other two in this group had an inferred erythrocytic volume greater than 40 ml per kilogram and, on this basis, might be suspected of having early polycythemia vera; one of these two had a normal PITR and the other a slightly increased PITR. Neither has been studied long enough to know in what diagnostic category each belongs, but the test predicts that one will prove eventually to have polycythemia vera and the other relative polycythemia.

TABLE 2.

SUMMARY OF IRON KINETIC DATA IN CONTROLS AND POLYCYTHEMIC PATIENTS

	Controls (6)	Relative polycythemia (14 patients)	Polycythemia vera (15 patients)
Mean PITR ±1 S.D., mg./kg./day	0.42 ±0.07	0.48 ±0.10	1.06 ±0.38
Mean $T_{½}$ ±1 S.D., minutes	105 ±26	76 ±26	21 ±9
Mean serum iron, micrograms/100 ml.	103	111	51

CONCLUSIONS

The plasma-iron turnover rate (PITR) is a useful adjunct in the differential diagnosis of polycythemia vera and relative polycythemia. It is particularly helpful in patients who demonstrate equivocal increases in erythrocytic volume.

When patients with polycythemia vera have been treated with radiophosphorus, the PITR can aid the clinician in deciding whether the patient is in remission or requires further treatment.

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The Radioisotope Renocystogram[1,2]

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INTRODUCTION

The Radioisotope Renogram is a tracer method for evaluating individual kidney function and patency of the upper urinary passages by external gamma ray scintillation counting techniques (1,2,3). Certain modifications have improved the Renogram since its introduction in 1956, when Diodrast I^{131} was used as the test agent. Liver intereference with the *right* renogram was eliminated by substituting test agents having no hepatic accumulation (4,5). Kidney localization by radiography was circumvented by employing collimated detectors with wide fields of view (6). Interpretation of individual tracings was enhanced by measurement of tracer excretion in 30 minute urine samples (7).

Nevertheless, the Renogram may be further improved in several ways. A test agent with more rapid renal turnover than agents in current use would increase the sensitivity of the Renogram for registering renal and upper urinary tract abnormalities. A quantitative external technique for measuring tracer excretion in the bladder would avoid the hazards of urethral catheterization and obviate errors of incomplete urinary collection. Finally, optimal arrangement and operation of detection equipment would guarantee more reliable and reproducible renal tracings.

This work is reported: 1) to demonstrate an efficient arrangement of detection equipment; 2) to describe qualitative and quantitative external techniques for measuring tracer excretion in the bladder; 3) to point out the superiority of I^{131}-labeled Hippuran, a new test agent recently introduced by Tubis (8); 4) to present typical findings with the latest techniques which portray the advantages of these refinements.

From the Laboratory of Nuclear Medicine and Radiation Biology, the Departments of Biophysics-Nuclear Medicine, Radiology, and Medicine, School of Medicine, University of California at Los Angeles, and the Nuclear Medicine Division, Radiology Service of the Los Angeles County Harbor General Hospital, Torrance, California.

[1]The investigations reported here were supported by Contract AT(04-1)-GEN-12 between the Atomic Energy Commission and the University of California at Los Angeles.

[2]Presented at the Seventh Annual Meeting of The Society of Nuclear Medicine, Estes Park, Colorado, June 25, 1960.

MATERIALS

The I^{131}-labeled test agents used in this study included iodopyracet (Diodrast), sodium diprotrizoate (Miokon), sodium diatrizoate (Hypaque) and sodium iodohippurate (Hippuran). These materials are all available commercially as sterile solutions having relatively high specific activity. These concentrated preparations may be diluted with sterile pyrogen free water or physiological saline to make up individual doses containing the desired amounts of test material and radioactivity. Dilutions to 1:500 do not alter renal turnover rates with any of these agents. The amount of urographic agent per test dose varies from micrograms to 30 milligrams, quantities which are at least 1000 times less than those used in radiography.

RENOCYSTOGRAM INSTRUMENTATION AND TECHNIQUE

Phantom studies were conducted to select the most practical arrangement of external scintillation detection equipment that would give reliable Renograms in the presence of high body background radioactivity. Three detector variables were measured: aperature diameter, length of crystal retraction within the cylindrical collimator, and lead filtration. Interference from the opposite kidney was also studied in addition to conditions simulating thin or obese patients.

The following conclusions were drawn from these experiments. 1) A detector aperature diameter of 2 1/2″, a crystal retraction of 2″ and no lead filter gave optimum arrangement of the equipment for efficient measurement of renal radioactivity with no interference from the opposite kidney. Geometry factors may be varied considerably and still permit accurate Renograms; however, smaller detector aperature diameters and greater crystal retraction made the positioning technique more critical. 2) Moving the kidney phantom 1.5 cm closer to the abdominal surface increased the count rate 25 per cent and positioning it 1.5 cm deeper decreased the count rate 18 per cent.

Fig. 1 illustrates the instrumentation for recording renal and bladder tracings. Both renal detectors have 1 1/2″ × 1″ thallium activated sodium iodide crystals housed in cylindrical lead shields 3/4″ thick and 9″ long and with inside diameters of 2 1/2″. The surfaces of these crystals are retracted 2″ from the openings of the shields. The bladder detector has a 2″ × 2″ NaI crystal housed in a similar shield. Its crystal is retracted one inch from the shield opening and is covered with a 0.5 mm thick lead filter. The three scintillation detectors are connected through precision ratemeters to recorders operated at chart speeds of one inch per five minutes. Tracer doses are selected to give sufficiently high count rates to permit statistically efficient operation of the rate meters with a two second time constant.

The patient is seated comfortably in the "Renogram chair" to assure immobilization during the test. The kidney probes are centered over the renal areas flush with the skin. The third detector aimed at the bladder is centered at the sacrococcygeal junction. Within 30-90 seconds after rapid tracer injection it is possible to reposition the renal probes if necessary. For example, if there are gross discrepancies between the heights of the two vascular segments and/or

differences in the slopes of the initial portion of the tubular segments, appropriate adjustments can be made to locate the area of maximum count rate.

The renal detectors are calibrated daily and adjusted to register the same level of radioactivity with a standard source. The tracer dose is measured in a syringe before and after injection in an I^{131} calibrated phantom. A test dose of 0.6 microcuries Hippuran I^{131} per kilogram of body weight is used to obtain peak count rates of 70,000-90,000 counts per miunte in normal subjects. The patient is not required to be in the fasting state but should be well hydrated. A *quantative in vivo* measurement of tracer excretion in the bladder is made immediately after completion of the ten to fifteen minute qualitative test.

Fig. 1. Photograph, showing renal and bladder probes in position and equipment employed.

QUANTITATIVE *IN VIVO* URINARY EXCRETION MEASUREMENT

Bladder phantom studies were made to select an optimum arrangement of detection equipment for obtaining accurate *in vivo* bladder measurements. The equipment is illustrated in Fig. 2. The detector has a 2″ × 2″ thallium activated sodium iodide crystal housed in the same type of shield as the renal probes. The surface of the crystal is retracted four inches from the opening of the shield to which a multistage collimator is attached. This arrangement eliminates body background and permits measurement primarily of bladder activity. The system is equipped with a projecting centering stick 60 cm in length. With the

patient positioned against a wall to secure immobilization, the centering stick of the detector is placed against the upper border of the symphysis pubis and pressure is exerted along its axis to insure a firm location at this bony landmark. Counts per minute are taken with a scaler. Tissue background is then measured over the upper posterior chest. Immediately after the patient has voided the bladder measurement is repeated to check for urinary retention. In normal subjects this technique provides count rates 8-12 times above tissue background values. The detector is calibrated daily with a standard bladder phantom the center of which is located 68 cm from the crystal surface. (The center of the

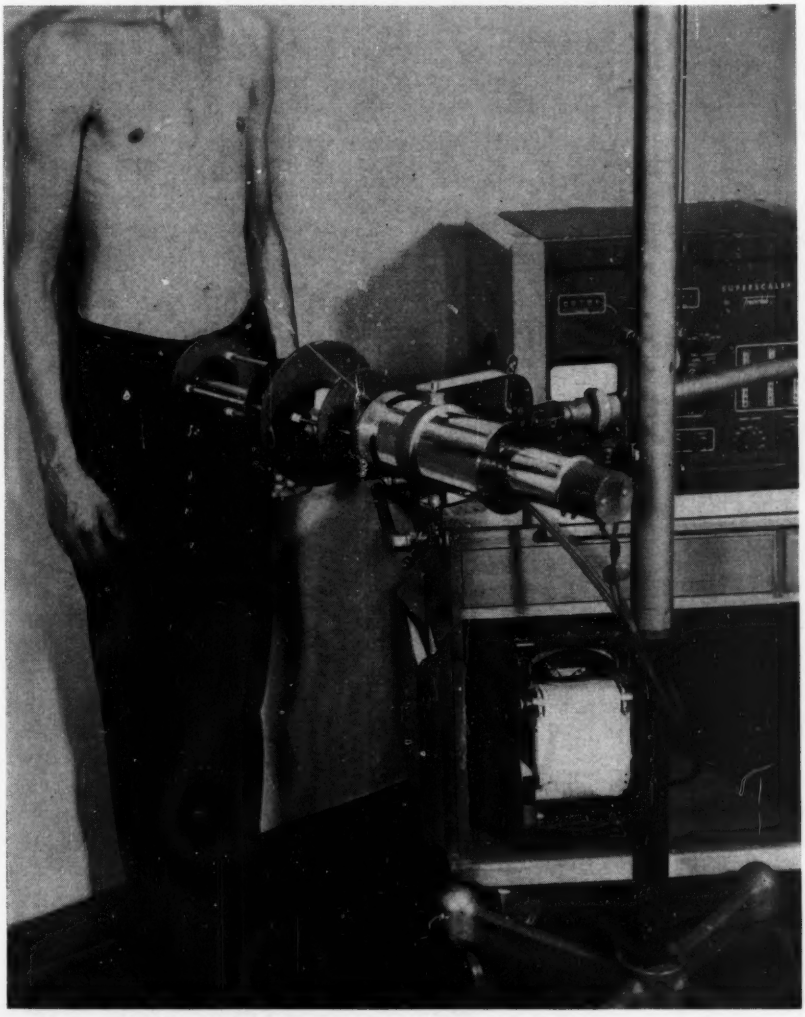

Fig. 2. Photograph, showing equipment in position for performing a quantitative in vivo measurement of bladder radioactivity.

urinary bladder in autopsy subjects is located 8.0 ± 0.5 cm from the anterior surface of the symphysis pubis.) The bladder measurement is calculated from this calibration (counts per minute per microcurie) and expressed as per cent of the administered dose. Errors made from excessively large bladder volumes (> 400 ml) are avoided by having the patient urinate prior to the test.

NORMAL DYNAMICS OF THE RENAL AND BLADDER TRACINGS

Renal and bladder curves each have three distinct segments (Fig. 3). The vascular segments (a) appear 15-20 seconds after injection of the tracer. The

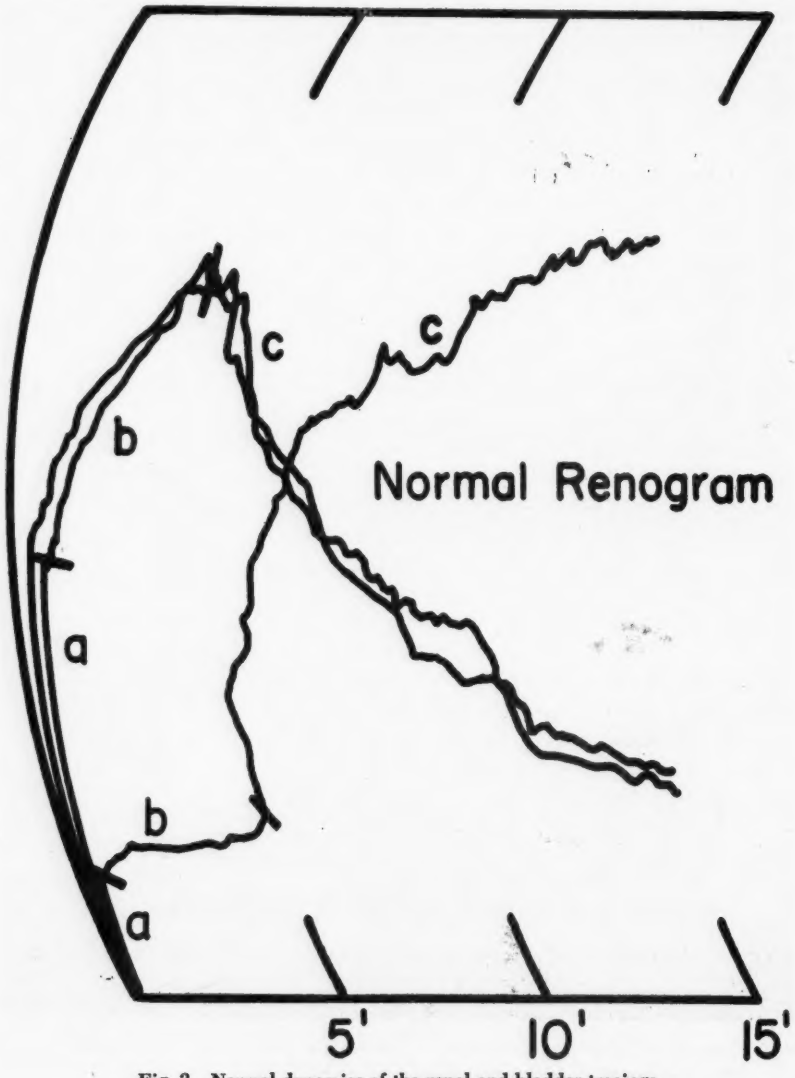

Fig. 3. Normal dynamics of the renal and bladder tracings.

bladder curve maintains a low plateau during the rising tubular phase of the renal tracings (b). This segment of the bladder curve represents kidney to bladder transit time. A sudden rise in bladder activity coincides with the onset of the renal excretion phase (c). This segment bears a reciprocal relationship to the renal excretion segments. There is a staircase-like rise in the *bladder accumulation segment* (c) which corresponds to a similar fall in the renal excretion segments. These intermittent changes in slope probably reflect ureteral peristalsis.

RESULTS AND INTERPRETATIONS

General

The present Renogram procedure with is supplemental bladder recording and quantitative *in vivo* measurement of tracer excretion has been employed during the past several months in the performance of 323 Renocystograms using a new test agent I^{131}-labeled Hippuran. Many of the subjects previously studied with Miokon, Hypaque, Diodrast and Renografin were re-examined with the augmented technique and new agent. Most of these patients were thoroughly investigated in the hospital with diagnostic procedures which included intravenous urography, retrograde pyelography, split renal function tests, and standard renal clearance tests.

Quantitative *in vivo* urinary excretion results

The validity of tracer excretion measurements by external scintillation counting over the bladder was tested by comparing values from the bladder movements *(in vivo)* with those from urine samples *(in vitro)* in fifteen control subjects and thirty patients having impaired renal function. The blatter record was marked to indicate the exact time when the quantitative measurement was made and again when the patient voided. Fifteen minute excretion values for both types of measurement were calculated from the extrapolated bladder accumulation curve. Fig. 4 illustrates the high degree of correlation between the two methods in both the control and renal disease groups (controls $r = 0.992$, $p < 0.001$; renal disease $r = 0.981$, $p < 0.001$). The standard error of the correlation coeffcient was 0.267 for the control and 0.200 for the renal disease group.

The mean fifteen minute tracer excretion (per cent of administered dose) of the control group by the *in vivo* method is 62.9 ± 5.7 per cent. The fifteen minute tracer excretion measurement as an index of overall renal tubular function is illustrated in Fig. 4 by the good separation of control values from those of patients with renal disease.

Comparative features of Diodrast, Miokon and Hippuran Renograms

The differing Renogram patterns of three urographic agents in the same normal subject are illustrated in Fig. 5. Hippuran's more rapid renal accumulation and excretion is reflected in the Renogram by more steeply rising and falling tubular and excretion segments. By marked contrast, the Miokon Renogram has rather shallow tubular and excretion segments and peak activity is reached

in 7.5 minutes compared with 2.5 minutes for Hippuran. Hippuran and Miokon Renograms have symmetrical right and left renal tracings in comparison with the asymmetrical curves obtained with Diodrast. Hepatic accumulation of Diodrast distorts the right renal record, especially in its excretion segment.

Typical abnormal Hippuran Renocystograms

The clarity with which functional renal abnormalities and obstructive lesions in the upper urinary tract may be depicted by the Hippuran Renocystogram is illustrated in the following examples.

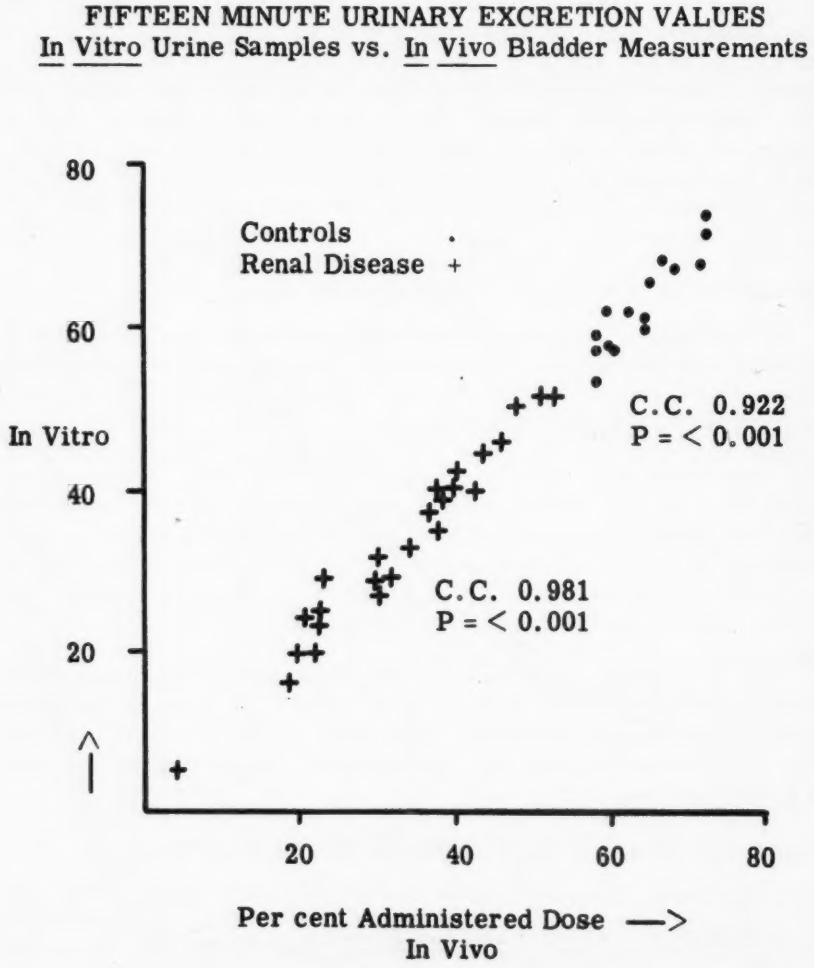

Fig. 4. Fifteen minute urinary excretion values (*in vitro* urine samples versus *in vivo* bladder measurements).

a) *Bilateral Renal Disease, Moderately Severe*

Fig. 6a shows the Hippuran Renocystogram of a patient with bilateral renal disease of moderate severity. The renal curves have sluggishly rising and falling tubular and excretion segments and peak radioactivity is reached later than in a normal subject. Impaired renal function is mirrored in the shallow slope of the bladder accumulation agent. Radioactive tracer enters the bladder as the downward slope of the renal curves begins, approximately seven minutes after intravenous injection. Accumulation of tracer in the bladder proceeds just as slowly as its discharge from the kidneys. These findings, when compared with a normal Renocystogram (Fig. 3), indicate moderate impairment of renal tubular function bilaterally. The fifteen minute tracer excretion was reduced to 41 per cent.

b) *Bilateral Renal Disease, Severe*

Fig. 6b illustrates how severely impaired renal tubular function produces very shallow tubular and excretion slopes in the renal tracings. The slow accumulation of tracer in the bladder as well as the 15 minute excretion of 15 per cent confirm the impairment of renal tubular function. The vascular segment of the bladder record is not altered by impaired renal function as are the vascular segments of the renal curves.

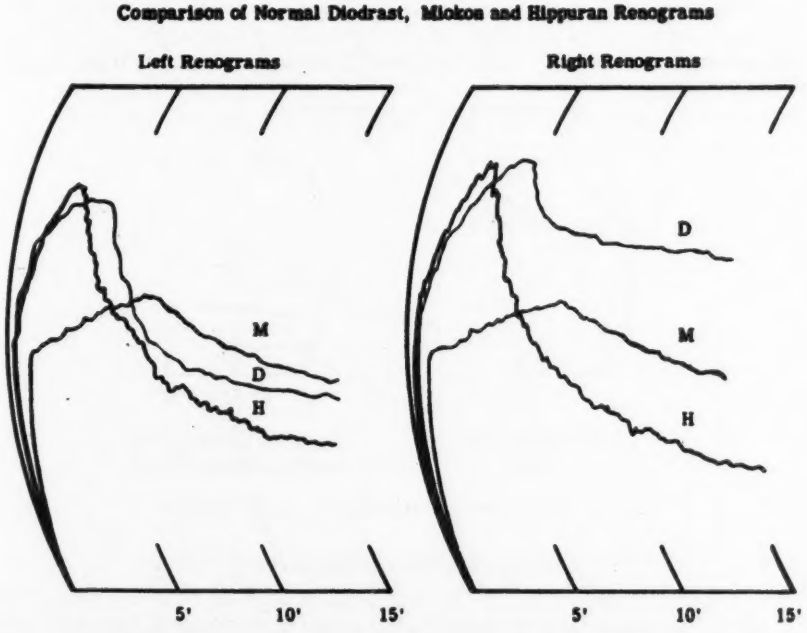

Fig. 5. Comparison of normal Diodrast, Miokon and Hippuran Renograms.

c) *Absent Right Kidney*

Fig. 6c shows a right kidney tracing with two distinct abnormalities. 1) The low magnitude of the vascular segment reflects the reduced vascularity in the region of the absent kidney. It reaches about one-half the height of its normal counterpart. 2) The immediate downward slopes of the curve indicates absent tubular function. The almost normal configuration of the bladder curve together with the normal left renal tracing would suggest that the left kidney had almost but not wholly compensated for the absent right kidney. The fifteen minute 53 per cent excretion of tracer affirms this interpretation. A nonfunctioning kidney gives a similar tracing except that the magnitude of the vascular segment is somewhat greater.

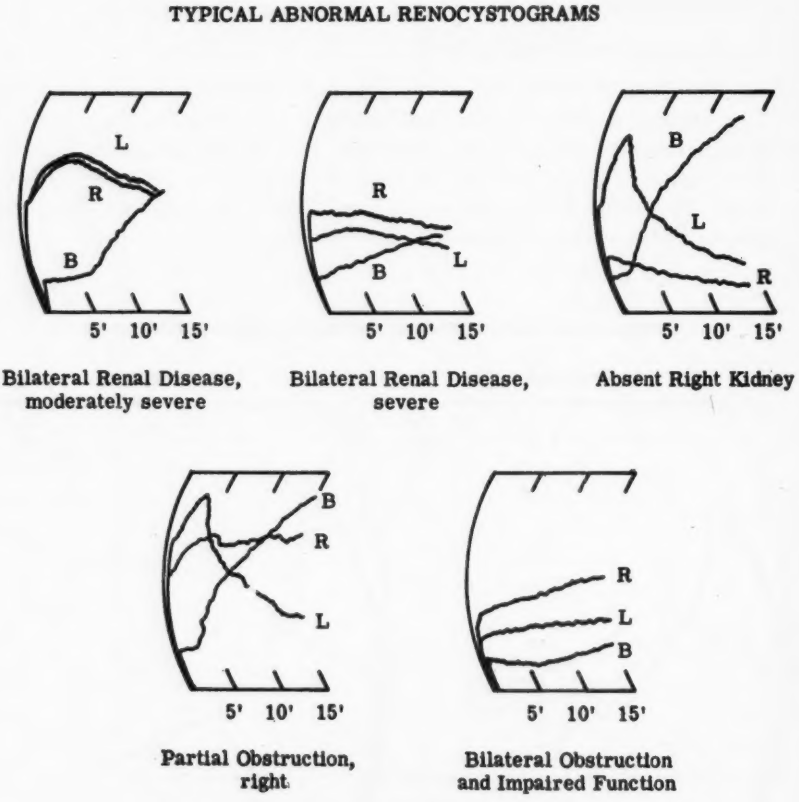

Fig. 6. Typical abnormal Hippuran I^{131} Renocystograms.

d) *Partial Obstruction and Impaired Function Right Kidney*

The Renocystogram in Fig. 6d represents a case of right hydronephrosis and pyelonephritis due to ureteropelvic junction obstruction. The right renal tracing has three abnormal features. 1) The slope of the tublar segment is

somewhat flattened indicating impaired tubular function. 2) Accumulation of radioactivity beyond the time when excretion normally begins indicates obstruction to outflow of urine from the right kidney. 3) Spasmodic changes in the excretion segment indicate partial obstruction and intermittent ureteral spasm. The abnormal bladder accumulation segment primarily reflects the delay in urinary excretion from the affected kidney. The 15 minute tracer excretion was reduced to 46 per cent.

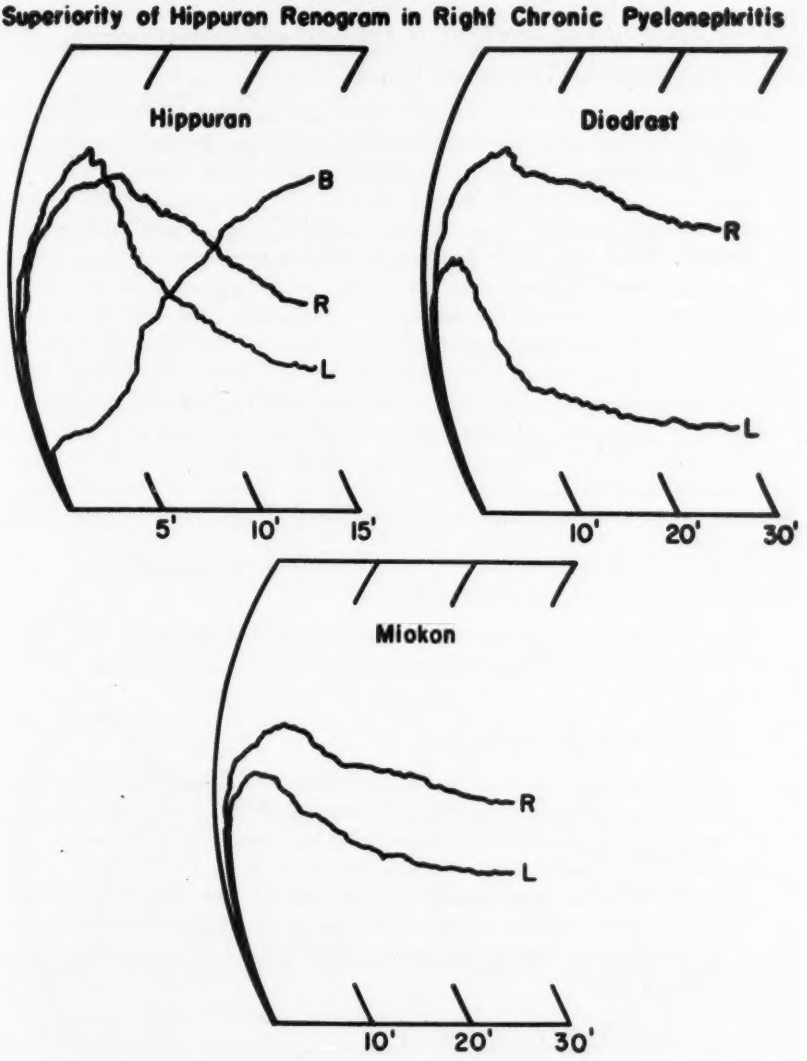

Fig. 7. Superiority of Hippuran over Diodrast and Miokon Renograms in chronic pyelonephritis.

e) *Bilateral Upper Urinary Tract Obstruction and Impaired Renal Function*

Fig. 6e illustrates renal tracings with two outstanding abnormalities. 1) The very shallow tubular segments reveal marked impairment of tubular function. 2) The continuous and prolonged rise in radioactivity indicates upper urinary tract obstruction. The appearance of tracer in the bladder *proves* that the obstruction is not complete. The 15 minute tracer excretion was 12 per cent.

Evidence demonstrating sensitivity of Hippuran Renocystograms

a) *Comparison with Other Test Agents*

Hippuran, by virtue of its rapid tubular cell turnover, increases the sensitivity of the Renogram for registering abnormalities of tubular cell function. Differing dynamic Renogram patterns of three test agents in the same abnormal subject are illustrated in Fig. 7. This patient has impaired renal tubular function of the right kidney due to chronic pyelonephritis. All three Renograms were performed within a three week period. The patient had been followed with serial Miokon Renograms for one year. In the Hippuran Renogram the difference between the right and left tracings is apparent. The ascending and descending slopes of the Right Renogram are conspicuously less steep than those of the left. Peak radioactivity on the right tracing occurs after that on the left. In the Miokon Renogram the difference in slopes and peak activities between the right and left records are present but less distinct. In the Diodrast Renogram the unilateral impairment of tubular function is obscured. Hepatic uptake of Diodrast has masked the abnormality in the excretory segment of the *right* renal tracing.

b) *Serial Hippuran Renocystograms*

The sensitivity of the Hippuran Renocystogram for depicting abnormalities of tubular function can be illustrated in patients who were tested in serial fashion.

1) ***Acute Nephritis (Toxic?)***

Fig. 8 shows a series of 4 Hippuran Renocystograms performed within a 20 day period on a patient with acute nephritis. The striking improvement in renal tubular function within this time is clearly demonstrated in the tracings by the progressive steepness of the tubular and excretion segments. The improvement is confirmed by the increasing steepness in the accumulation segments of the serial bladder tracings and by the increase in the 15 minute excretion values of tracer from 22.5 to 50.2 per cent.

2) ***Acute Right Pyelonephritis***

Fig. 9 shows serial Hippuran Renograms on a patient during a 36 day period. Normal right and left renal tracings were recorded on 3-9-60.

When the second Renogram was performed on 3-24-60, the patient was having an attack of acute right pyelonephritis. The right renal tracing shows a prolonged tubular segment with little if any diminution in slope. On 4-5-60 there is a staircase descent pattern to the excretory segment of the right renal tracing. This precipitous, intermittent descent suggests ureteral spasm secondary to inflammation. The Renogram of 4-16-60 is approaching the norm.

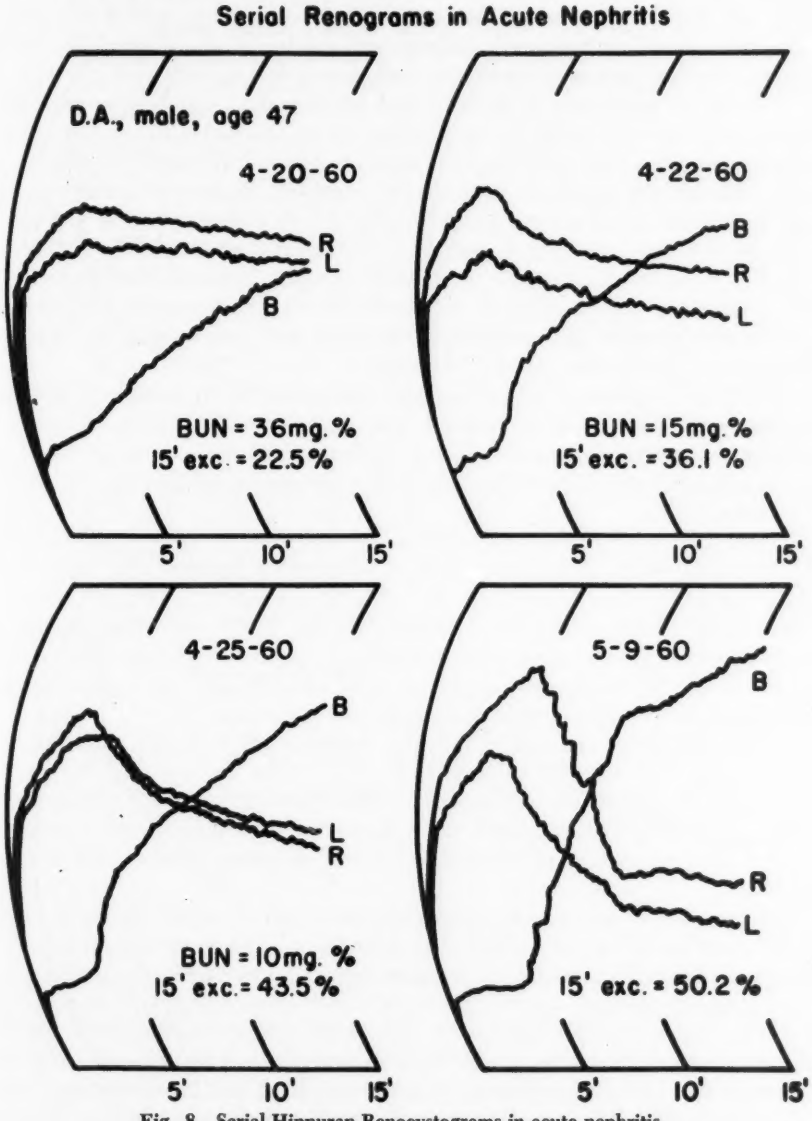

Fig. 8. Serial Hippuran Renocystograms in acute nephritis.

DISCUSSION

The principles of the Radioisotope Renogram were established originally on a physiological basis from tracer studies in rabbits (1). Magnusson (9) used the Renogram technique in conjunction with radioautography to investigate the renal distribution and transport of Diodrast I^{131}. Serial radioautograms of frozen kidney sections 2 to 55 minutes after Diodrast injection demonstrated the validity of external Renogram measurements at the cellular level. These principles were substantiated by the thorough clinical investigations of others who found a close correlation between Renogram findings and results of examination by radiography, standard laboratory procedures and autopsy (10, 11, 12).

From an evaluation of physical and physiological variables in Renogram phantom studies, an optimum arrangement of equipment and technique to obtain consistently satisfactory renal tracings was selected. It should be pointed out that with the new test agent Hippuran I^{131} detector geometry is much less critical. Satisfactory renal tracings can be obtained with detectors having little or no shielding. A servo-recorder is available commercially which permits both renal tracings to be inscribed on the same graph. A fast (2 second) time constant in the ratemeters permits accurate registration of rapidly changing physiological events. For example, the intermittent retention and release of urine from the renal pelves (peristalsis) is clearly depicted.

A graphic record of tracer accumulation in the bladder helps to interpret events occurring in the renal tracings. The renal tracings in Fig. 6e, an example of bilateral ureteral obstruction, show a continuous and gradual rise. It would not be possible to know without the help of the bladder record that the obstruction was incomplete.

The 15 minute *in vivo* and *in vitro* measurements of tracer excretions have nearly equal values when determined in cooperative patients who are able to empty their bladders completely. However, in patients in whom collection of urine is not reliable or who have urinary retention, the *in vivo* measurements are more accurate. Several patients with urinary retention were examined by both methods, and the *in vitro* measurement (urine sample) plus the residual *in vivo* measurement correlated well with the initial *in vivo* value.

The 15 minute quantitative bladder measurement of tracer excretion is a sensitive index of overall renal tubular function. These findings with the *in vivo* technique confirmed our previous work which showed that the measurement of tracer excretion in 30 minute urine samples was a more sensitive index of overall renal function than either tracer blood clearance or 30 minute PSP excretion (7).

Hippuran, by virtue of its rapid renal turnover and organ specificity, is the ideal tracer agent for the Radioisotope Renogram. The greater sensitivity of the Hippuran Renogram in detecting renal and upper urinary tract abnormalities has been demonstrated by comparative studies with other test agents in the same patients and by serial Renograms in individuals with fluctuating renal disease.

The present Renogram proceduer with supplemental bladder recording and quantitative *in vivo* measurement of tracer excretion has broadened the scope of the original Radioisotope Renogram. It provides data from which evaluations

of individual and overall kidney function as well as upper urinary tract patency may be made. The quantitative bladder measurement made at the end of the test period (15 minutes) extends the applicability of the procedure to that of a multipurpose tracer test for investigating all patients with suspected disease of the urinary system. The combination of external renal and bladder measurements of tracer accumulation and excretion might appropriately be named the Renocystogram.

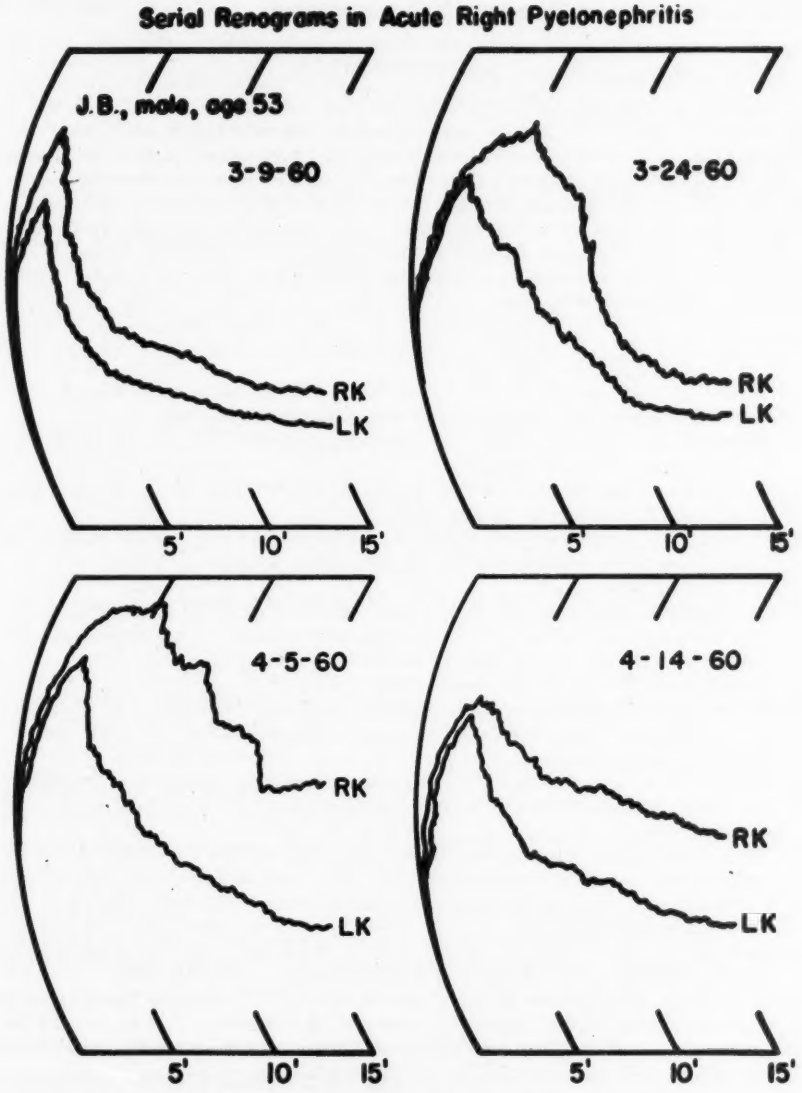

Fig. 9. Serial Hippuran Renograms in acute, right pyelonephritis.

SUMMARY

1. An optimum arrangement of external scintillation detection equipment for obtaining reliable Renograms has been described. Considerable latitude in this area is permissible.
2. I^{131}-labeled Hippuran has been a major factor in the improvement of the Radioisotope Renogram.
3. The conventional Renogram has been developed into a multipurpose radiotracer test called the Hippuran I^{131} Renocystogram.

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CALENDAR OF EVENTS

Date	*Name of Course or Meeting*	*Place*
April 16-19	German Roentgen Society	Hamburg, Germany
April 17-19	Conference on Nuclear Physics	Birmingham, UK.
April 18	*Southern California Chapter*	*Los Angeles*
April 19	*Eastern Great Lakes Chapter*	*Toronto, Canada*
April 24-27	American Physical Society	Washington, D.C.
April 30	American Federation for Clinical Research	Atlantic City, New Jersey
May 3-6	American Goiter Association	Philadelphia, Pennsylvania
May 8-10	National Power Instrumentation Symposium	Chicago
May 9-11	Conf. on Aspects of Internal Irradiation of Mammals	Saratoga, Wyoming
May 11-14	American Radium Society	Colorado Springs, Colorado
May 15-17	9th Annual Meeting, Radiation Research Society	Washington, D. C.
May 15-26	Radiological Health for Nurses	Rockville, Maryland
June 3-11	Meeting on Radiotherapy with High Powers—in conjunction with the 4th International Medical-Surgical Film Festival	Turin, Italy
June 4-8	American Nuclear Society	Pittsburgh, Pennsylvania
June 13-16	Symposium on Whole Body Counting	Vienna, Austria
June 14-17	*Society of Nuclear Medicine*	*Pittsburgh, Pennsylvania*
June 22-24	The Endocrine Society	New York, New York
June 22-24	American Physical Society	Mexico City
June 26-30	American Medical Association Section on Radiology	New York City
July 16-22	4th International Conference on Bio-Medical Electronics	New York City
August 1-4	International Congress of Biophysics	Stockholm, Sweden
August 6-26	Summer Course in Nuclear Physics	Varenna, Italy

(Continued on page xi)

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Evaluation of Portal Circulation by Percutaneous Splenic Isotope Injection[1]

Robert H. Greenlaw, M.D.[2] and Seymour I. Schwartz, M.D.[3]

Rochester, New York

INTRODUCTION

The evaluation of the circulatory dynamics in the portal venous system presents certain difficulties. This is true particularly in the situation of massive, upper gastro-intestinal bleeding. Radiological studies with barium many times fail to reveal varices, especially during a period of emergency. Splenoportography is a sufficiently involved technique to make it impractical, if not hazardous, when used other than as an elective procedure.

Results from splenic injection of isotope tracers in multiple animal studies and in ten patients appear to offer a technique which circumvents many of the above problems.

MATERIALS AND METHODS

In these studies, a dual detection system[4] is utilized (Fig. 1). This makes use of twin scintillation probes, twin rate meters, and twin chart recorders. One detector is placed over the liver and directed slightly laterally. The second detector is placed over the right side of the heart-right lung root area and includes in its field of response the middle section of the esophagus. Rate meters are operated at 0.5 second time constants. Recorders are run at a speed of 12 inches per minute. The recorders can respond with full scale deflection in 250 milliseconds, thereby adding no significant delay to the response of the rate meters.

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1. From Departments of Radiology and Surgery, University of Rochester Medical Center, Rochester 20, New York.

Presented at the Seventh Annual Meeting, The Society of Nuclear Medicine June 25, 1960.

2. Scholar of the James Picker Foundation in Radiological Research during the initial part of this work. Currently, Advanced Clinical Fellow in Radiation Therapy under the American Cancer Society.

3. Markle Scholar.

4. Picker Dual Detection System.

Although several types of tracer materials have been used, an agent with a very short biological half-life, such as Radiorenographin,[1] appears most satis-

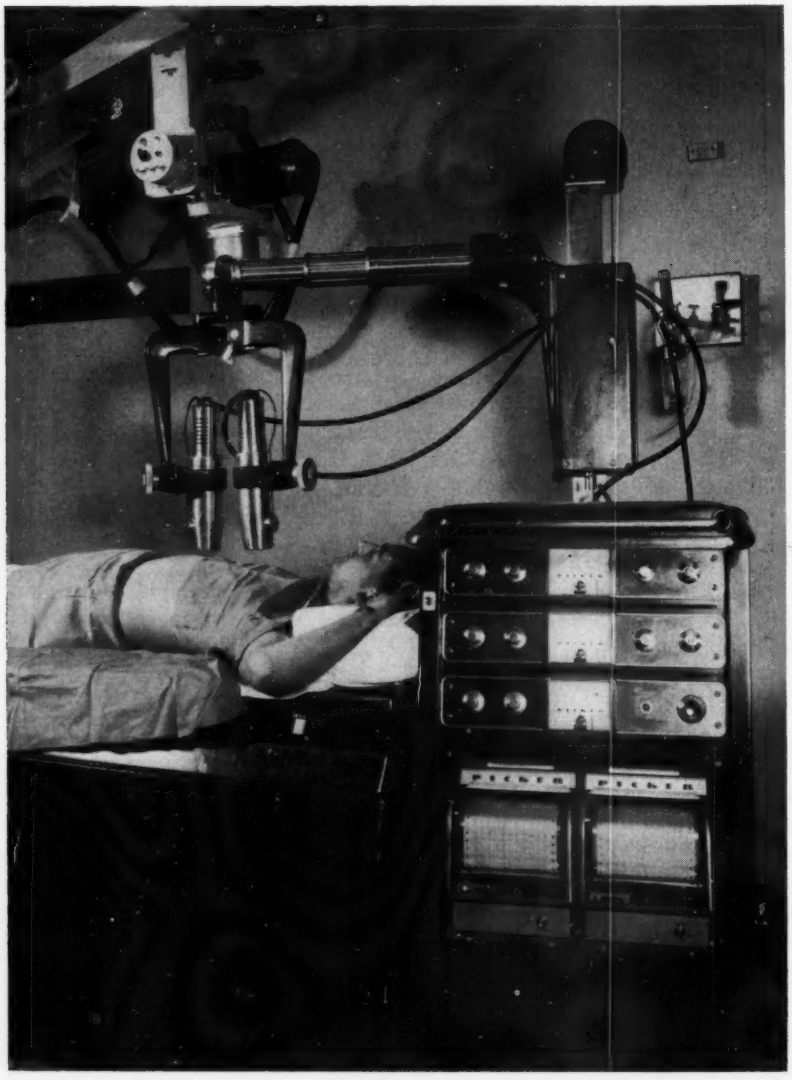


Fig. 1. Twin detectors in place over the liver and heart. X-ray tube in background may be moved into position for splenoportal radiography after the isotope studies.

factory. The study can be accomplished easily with 30 μc of radioiodine contained in a volume of 0.5 ml or less.

1. E. R. Squibb.

Details of the technique were worked out in six dogs after laparotomy for exposure of the spleen and the liver. Results gave excellent correlation with the known physiologic situation in the animals.

CLINICAL STUDIES

Clinically, thus far, this procedure has been done in conjunction with the measurement of the splenic pulp pressure and splenoportal radiography. Using local anesthesia, splenic puncture is made in the left, ninth intercostal space between the middle and posterior axillary lines.

Correlation of results with splenic pulp pressure and with splenoportal radiograms in various clinical situations can best be seen in sample case presentations:

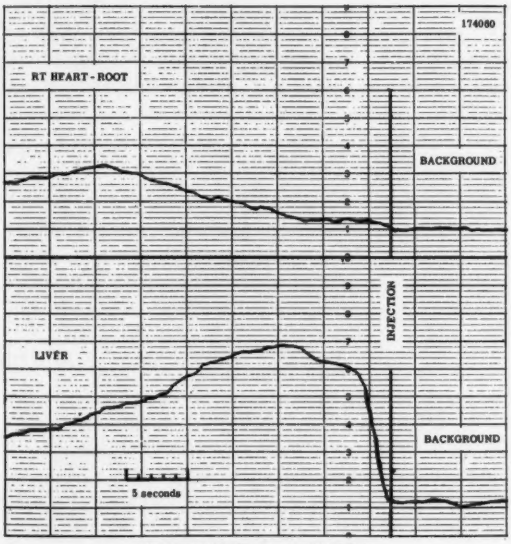


Fig. 2a. Recordings of activity in normal portal flow. Read from right to left.

Case One (E. S. #174060).—Gastro-intestinal bleeding with normal portal studies.

A 47 year old male with massive upper gastro-intestinal bleeding, presented a problem in differential diagnosis. Although previous hospitalizations had failed to reveal evidence of liver disease, this man was known to be a "binge" drinker. The current bleeding developed during a drinking episode. At the time of admission, the liver was slightly enlarged, the prothrombin time was 50 per cent, total bilirubin was 2mg per cent, and thymol turbidity was 3 plus. Other blood chemistries reflecting liver function were not significantly altered. An emergency upper gastro-intestinal x-ray examination was done, but neither esophageal varices nor peptic ulcer could be definitely demonstrated. Suspecting varices, the period of emergency was managed with a Sengstaken-Blakemore tube and gastrostomy. Gastroscopy through the abdominal wound at the time of operation failed to reveal a definite bleeding site. After multiple transfusions, bleeding gradually came under control. With appropriate

therapy, the blood chemistries returned to normal. Repeat gastro-intestinal X-ray examinations on two occasions during the month of hospitalization revealed a duodenal ulcer. Varices were never found. One month after admission, when the patient was clinically normal, splenoportography was done. Splenic pulp pressure of 200 mm of saline was found. Isotope studies (Fig. 2a) showed the appearance of the tracer material in the liver within 0.5 seconds from the time of injection. Peak activity was found at 3 seconds, followed by a steady decline in tracer concentration. Radioactivity was detected in the heart at 8 seconds following which the rate of increase was the inverse of the decline in liver activity. Splenoportography was normal (Fig. 2b).

This patient had fatty infiltration of the liver, which with therapy, had essentially cleared. The duodenal ulcer may well have been the only site of bleeding, and may have been aggrevated by the slightly increased portal venous pressure.

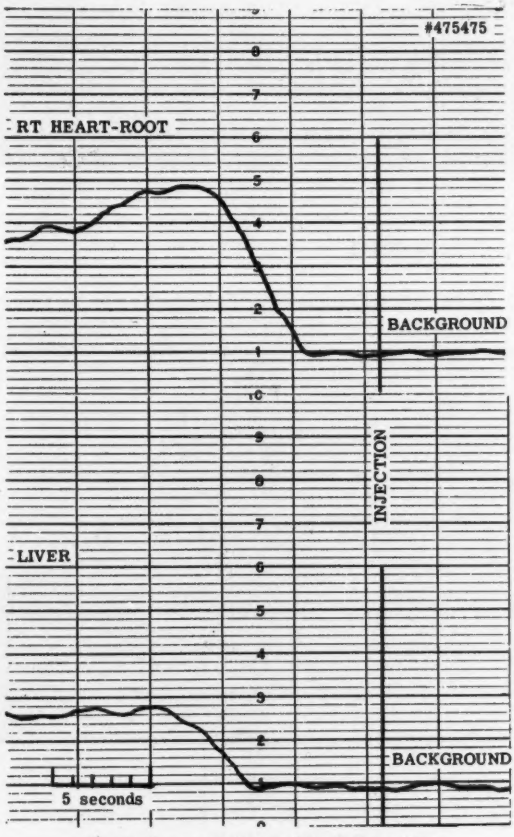
Fig. 2b. Splenic pulp injection of contrast material. Normal splenic vein, portal vein and arborization in liver are seen. No collateral venous pattern.

Comment: In normal splenoportal circulation activity appears earlier in the liver and peaks higher than in the heart area.

Case Two (A.K. #475475)—Intra hepatic and extra hepatic obstruction.

A 57 year old female was admitted with hematemesis. The patient was a non-drinker who had a cholecystectomy one year previously. There had been recurring fever and upper abdominal pain since surgery and an interim re-exploration had been done. This revealed dense adhesions about the common duct. Liver biopsy at that time showed hepatitis and focal necrosis.

When admitted for bleeding, the liver and spleen were enlarged. The serum alkaline phosphatase was elevated to 19 Bodansky Units, and the cephalin flocculation was 3 plus. Gastro-intestinal X-ray examination revealed esophageal varices. At percutaneous splenic puncture, a pulp pressure of 340 mm of saline was found. Isotope studies (Fig. 3a) showed tracer material appearing in the heart in slightly less than 4 seconds, rising rapidly, then falling rapidly after reaching a peak at 9 seconds. Tracer material appeared in the liver at 7 seconds, reached a rather low peak at 11 seconds where it remained for 15 seconds before declining slowly. Splenoportogram (Fig. 3b) showed dilatation of the splenic vein, retrograde flow into mesenteric vessels, and a prominent collateral network about the esophagus. No opacification of the portal vein was seen.



100 micro curies I-131 as ISA, 0.5 sec time constant, 100 K max. response, 12 in/min

Fig. 3a. Recordings of activity on hepatic obstruction with portal hypertension and varices. Read from right to left.

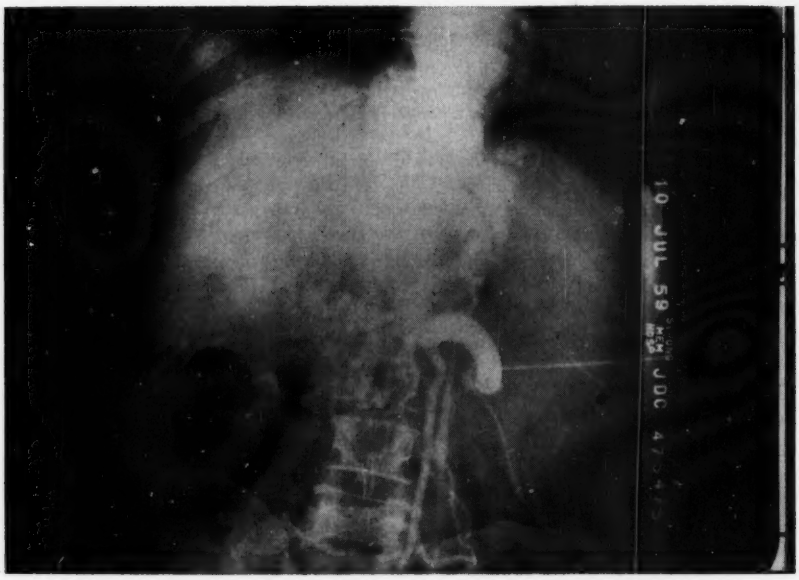


Fig. 3b. Splenic vein injection of contrast material. Splenic and portal veins are dilated; reflux is seen in mesenteric vessels. Coronary vein of stomach and esophageal network are well demonstrated.

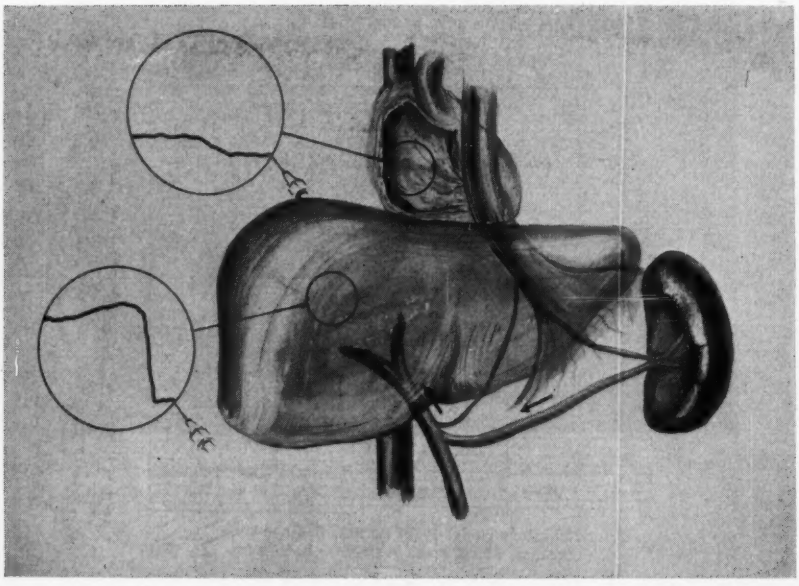


Fig. 4. Splenoportal flow pattern in the normal situation with representative recordings over liver and heart.

At operation, the porta hepatis was encased by dense fibrous scarring. Liver biopsy showed acute and chronic cholangitis.

Although the portal vein was not opacified, tracer studies showed a minimal portal blood flow.

Comment: Intra hepatic obstruction to portal flow is rarely complete. This situation shows delayed appearance of tracer in the liver, low peak of activity and plateau. Extra hepatic portal obstruction is frequently due to thrombosis and thus is complete. In this instance no activity would appear in the liver except from arterial supply.

DISCUSSION

The adoption of a new procedure using radio-isotopes is difficult to justify unless it can be shown to do a task better, or is less hazardous, than a procedure currently in use. The problems and hazards of splenoportography are well known. Compared with splenoportography, the radioisotope technique reported is inexpensive in materials and time. It can be done quickly and easily. The injection of 0.5 ml of tracer material approaches physiologic conditions and can be achieved through a small-bore, flexible needle with negligible trauma to the spleen and its capsule. It is a portable procedure. It can be done under emergency conditions to evaluate the possibility of varices. It also promises to be a useful elective procedure for the evaluation of splenic enlargement of unknown etiology; as a check on the position of the needle prior to splenoportography; and as an indicator for the proper timing sequence in splenoportal radiography.

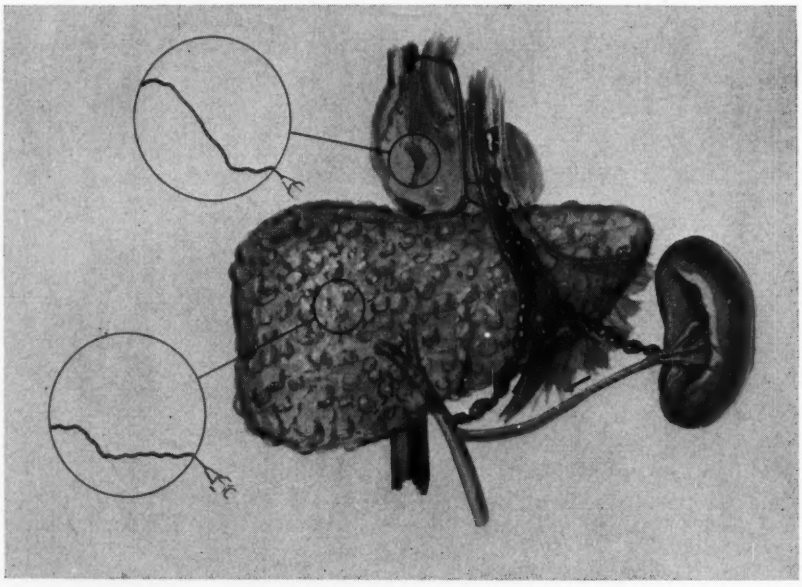


Fig. 5. Splenoportal flow pattern in intra hepatic obstruction, showing collateral channels. Recordings over liver and heart are representative.

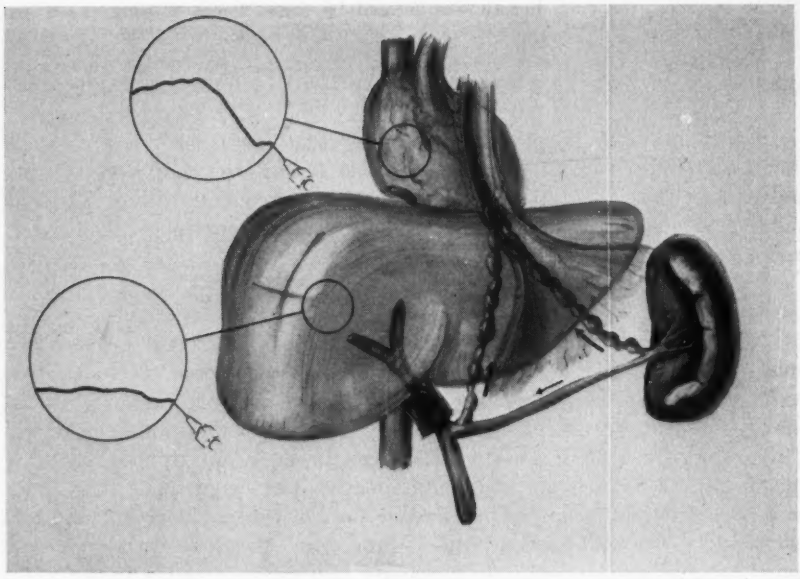


Fig. 6. Splenoportal flow pattern in extra hepatic obstruction, showing collateral channels. Recordings over liver and heart are representative.

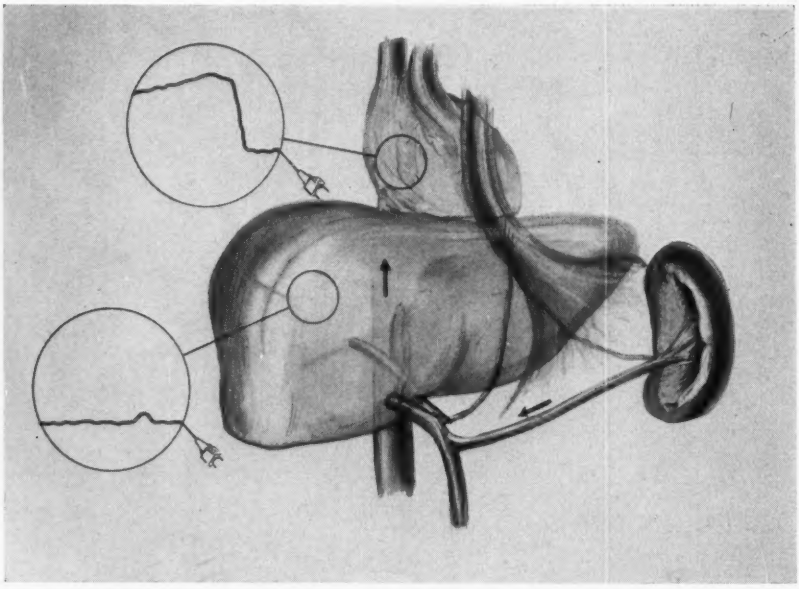


Fig. 7. Flow pattern with splenoportal shunt. Recordings over liver and heart are representative.

TABLE 1

COMPARATIVE VALUES FOR LIVER AND HEART

	LIVER			HEART		
	Appearance	*Peak*	*Decline*	*Appearance*	*Peak*	*Decline*
Normal (Fig. 4)	0.1-1.0 sec	2-6 sec	Fairly Rapid	6-10 sec	12-22 sec	gradual
Intra hepatic Obstruction with varices (Fig. 5)	1-3 sec	6+ sec	Plateau	1-6 sec	4-8 sec	rapid
Extra hepatic Obstruction (thrombosis) with varices (Fig. 6)	Much delayed, if detected			1-6 sec	4-8 sec	rapid
Portocaval Shunt (Fig. 7)	0.1-4 sec	3-6 sec (IVC)	Very Rapid	4-7 sec	7-10 sec	rapid

Diagnosis of the etiology of altered portal circulatory dynamics by means of this test is based on rather major quantitative differences between the two areas measured. Gross circulation times may vary depending on whether injection is into splenic pulp or into the splenic vein. Comparative values for various conditions are presented in Table 1.

SUMMARY

A technique of splenic isotope injection for the evaluation of portal circulatory dynamics has been presented. By tracing circulation to the liver and heart, considerable information can be gained concerning portal hypertension, speed of hepatic blood flow and the presence of collateral venous return.

ACKNOWLEDGEMENT:

Constructive criticism of the manuscript by Dr. Philip Rubin is gratefully acknowledged.

JOURNAL OF NUCLEAR MEDICINE 2:94, 1961

A Note on the Formulation of Iodine-131 Labelled Polyvinylpyrrolidone for Intravenous Administration

by

William H. Briner[1]

Bethesda, Maryland

The need for a macromolecular, biochemically inert substance suitable for human use as a diagnostic agent in determining qualitatively the differences between true hypercatabolic hypoproteinemia, exudative enteropathy, and certain other disease states involving either insufficient albumin production or an excessive loss of albumin due to any of several causes is easily demonstrated in recent medical literature (1, 2, 3). It is readily apparent that the mechanism of protein production, catabolism, and loss due to other causes are all rather important considerations in the evaluation of patients with these several protein disorders.

Gordon offered to the scientific community a notable advance in definitive diagnostics when he originally described a method of preparation of radioactive polyvinylpyrrolidone for medical use (4) and subsequently outlined his preliminary clinical experience with this compound (5). While this material does not satisfy all the desirable criteria for such a product, it was indeed a most welcome step in the right direction, for many of the conditions suggested by Luck (1) in his editorial are fulfilled by this compound. The method of pharmaceutical formulation herein described is a modification of the original method described by Gordon, with certain more recent innovations designed to improve the radiochemical yield and pharmaceutical quality of the final product.

The structure of PVP-I^{131} is diagrammed below.

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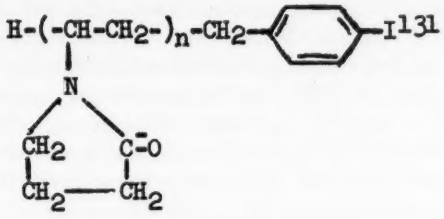
1. From Radiopharmaceutical Service, Pharmacy Department
Clinical Center, National Institutes of Health
U. S. Public Health Service
Department of Health, Education and Welfare
Bethesda, Maryland



As is apparent from this structure, PVP is a linear polymer, the n indicating that the monomeric unit, vinylpyrrolidone, occurs many times in each chain, while the iodine label occurs only once, at the termination of each chain. In order to preclude the possibility of lower molecular weight polymers of PVP diffusing from the circulation into the gastrointestinal tract, an attempt was made to remove the lower molecular weight fractions of the polymer. This was accomplished by dialyzing an aqueous solution of 100 grams of the polymer against constantly changing pyrogen-free distilled water for a period of eight hours in Visking Cellulose Tubing [a]. The polymer solution remaining inside the dialyzing tubing was then sterile filtered through a Millipore membrane filter of 0.45 micron maximum pore size [b], and subsequently aseptically transferred into sterile serum vials in volumes such that the material placed in each vial represented approximately 1.5 Gm of dissolved polymer. Under sterile conditions, the vials were then lyophilized on a VirTis Macro Freeze-Dryer [c] and stored in a vacuum desiccator at —4° for future use. It is believed that this pre-formulation dialysis is, in large measure, responsible for the increase in our raidochemical yields from a former range of 20-25 per cent to a normal yield of about 35 per cent on recent batches.

Each lot of IODO-PVP (I-131) INJECTION is prepared as follows. One lyophilized unit of PVP, representing approximately 1.5 Gm of dry polymer, is dissolved in 10 ml of 0.2N sulfuric acid and chilled in an ice bath. A 10 per cent w/v solution of sodium nitrite in pyrogen-free distilled water is prepared, and a sufficient amount of this solution to supply 1 mg of sodium nitrite for each mg of dissolved solids shown to be present in the NaI^{131} to be utilized in the formulation is added to the acidic solution of the polymer. An amount of NaI^{131} solution [d] equivalent to approximately 100 millicuries of I^{131} is placed in a transparent fused quartz cell [e] (Fig. 1) and the diazotized polymer-nitrite solution is immediately added to the radioisotope. The quartz cell is then stoppered and irradiated with a Hanovia ultraviolet light [f] of 2537 Angstrom wave length for 30 minutes. During the period of irradiation, the quartz cell is positioned with a flat side of the cell in a plane perpendicular to the primary beam emanating from the ultraviolet lamp at a distance of approximately 5 centimeters (Fig. 2). While the irradiation is taking place, a stream of cool compressed air is directed against the bottom of the quartz cell to prevent excessive heating of the contents.

After irradiation, the quartz cell is again chilled in an ice bath. The contents of the cell are then alkalinized with 1.0 ml of ammonium hydroxide solution, 38 per cent. Then, add 100 mg of sodium sulfite previously dissolved in 2 ml of

pyrogen-free distilled water. The contents of the quartz cell are then transferred to a suitable length of cellulose dialysis tubing [a] and dialyzed for a period of six hours against a solution containing sodium sulfite, 1.0 Gm; potassium iodide, 5.0 Gm; sodium bicarbonate, 100.0 Gm; in sufficient pyrogen-free distilled water to make six liters. It is advisable to change the dialyzing solution at least once during this period. The dialyzer is then drained, and the material in the dialyzing tubing dialyzed against constantly changing pyrogen-free distilled water for an additional period of 15 hours.

After dialysis is completed, the labelled polymer solution is passed through an ion exchange column packed with Amberlite IRA-400 anion exchange resin [g] to remove unbound iodide remaining in the solution. At this point, an estimate of the radiochemical yield is obtained by calibrating the radioactivity in the product against a suitable standard using a Lauritsen electroscope.

A measurement of the volume of the product is then made, and any desirable adjustment of the volume accomplished with pyrogen-free distilled water, depending upon the final radiochemical concentration desired. Anhydrous dextrose is added so that the concentration in the final product is 5 per cent; an addition of benzyl alcohol as a bacterial preservative to a final volume concentration of 0.9 per cent is also made. The product is then subjected to a clarifying filtration through a 1.2 micron Millipore membrane filter [b] and packaged in suitable serum vials of Type I USP glass. Sterilization of the final product is accomplished by autoclaving at a temperature of 121° C at a pressure of 18 psi for 15 minutes.

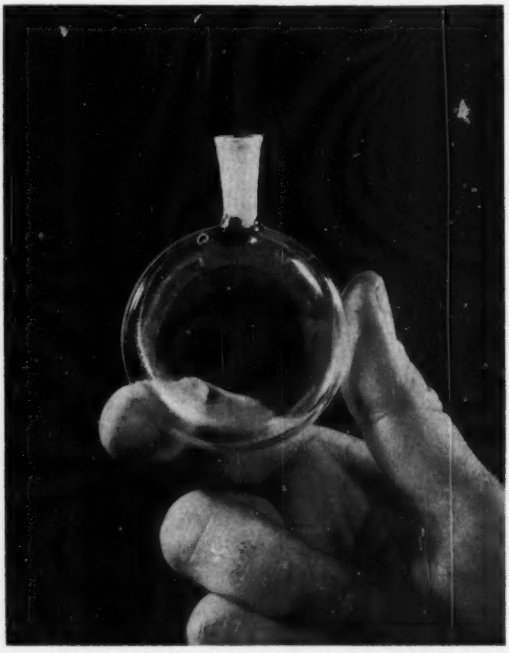


Fig. 1. Fused quartz cell in which PVP-I^{131} is irradiated with ultraviolet light.

The product is then subjected to pyrogen and sterility testing as outlined by the United States Pharmacopeia (6) and an accurate radiochemical assay in microcuries of I^{131} per milliliter of finished product performed using suitable instrumentation. Finally, an estimate of the unbound or loosely bound iodide present in the product is obtained by passing an aliquot of the finished product through an ion exchange column, again packed with Amberlite IRA-400 resin [g], and comparing the radiochemical assay of the effluent from the column with that of the final product as previously determined. Unbound or loosely bound iodide in batches of IODO-PVP INJECTION in recent months has approximated 1.5 per cent as determined by this method. The iodine bond to this polymer of PVP is apparently quite a strong one, and is not to be confused with certain commercially available topical antiseptics utilizing a complex of polyvinylpyrrolidone with iodine. In the latter case, the iodine present in the complex is relatively easy to release. The Fikentscher K values for recently prepared batches have been in the range of 25 to 35. The relationship of K value to biological behavior has been discussed by Ravin, Seligman, and Fine (7).

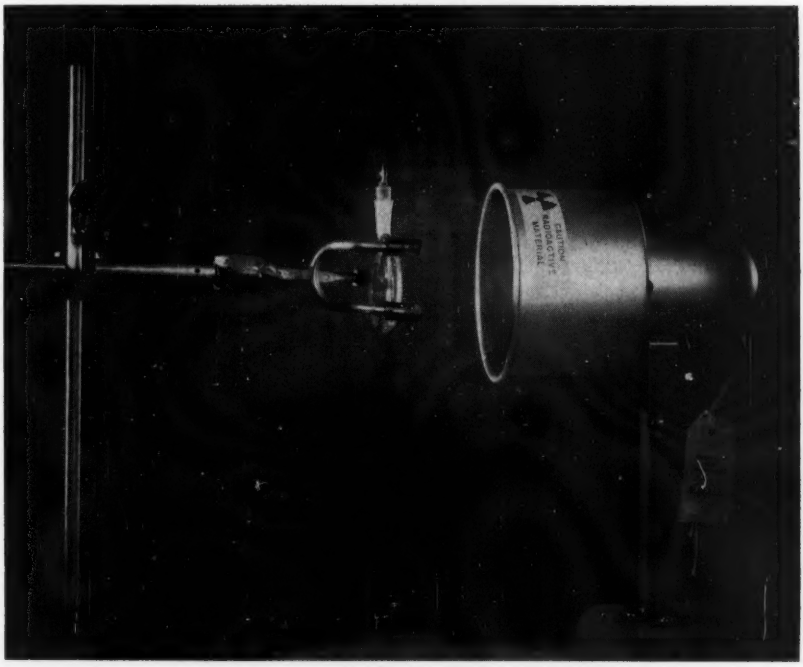


Fig. 2. Proper positioning of fused quartz cell in front of ultraviolet light source.

[a]Available from the Visking Co., Chicago, Ill.
[b]Available from the Millipore Filter Corp., Bedford, Mass.
[c]Available from the VirTis Co., Inc., Gardiner, N.Y.
[d]Obtained from Oak Ridge National Laboratory, Oak Ridge, Tenn., as I-131-P.
[e]Available from Fisher Scientific Co., Silver Spring, Md.
[f]Available from Hanovia Chemical and Mfg. Co., Newark, N.J.
[g]Available from Fisher Scientific Co., Silver Spring, Md.

SUMMARY

A method for the labelling of polyvinylpyrrolidone with iodine^{131} and the formulation of this radiochemical into a suitable radiopharmaceutical dosage form is presented. For records of clinical experience with this compound, the reader is directed to the references and the general bibliography.

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JOURNAL OF NUCLEAR MEDICINE 2:99, 1961

Superimposed Optical and Gamma-Ray-Scanner Images[1,2]

Hal O. Anger and George M. Tisljar-Lentulis[3]

Berkeley

Whole-body gamma-ray scanning has been used for some time to locate functioning thyroid tissue in patients suspected of metastatic thyroid disease. The patient is given a tracer dose of I^{131}, and 24 to 96 hours later he is scanned to de-

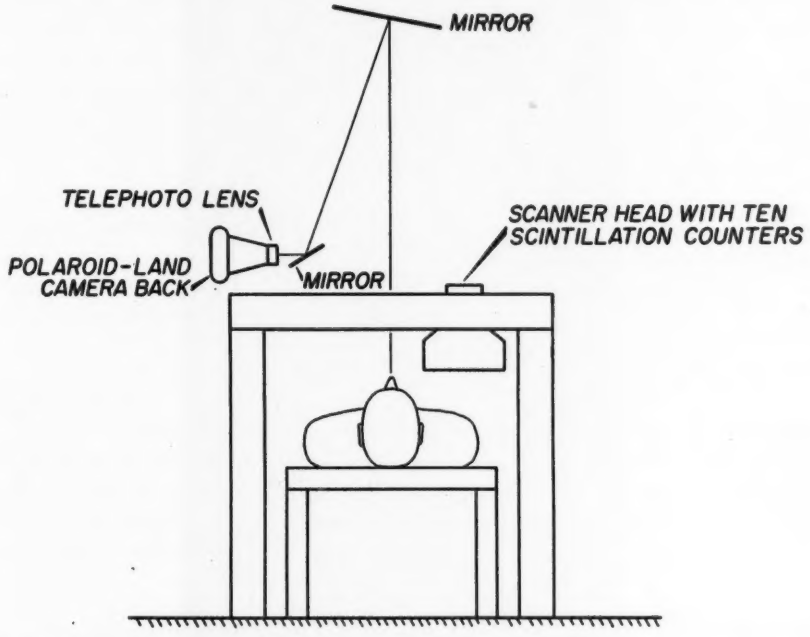

Fig. 1. Optical apparatus mounted to give vertical view of patient.

1. From the Donner Laboratory and Lawrence Radiation Laboratory, University of California, Berkeley.

2. This study is based on work performed under contracts with the U.S. Atomic Energy Commission.

3. Fellow from the First Physics Laboratory, University of Vienna, Austria. Appointment supported by the International Cooperation Administration under the visiting research scientists program administered by the U.S. National Academy of Sciences.

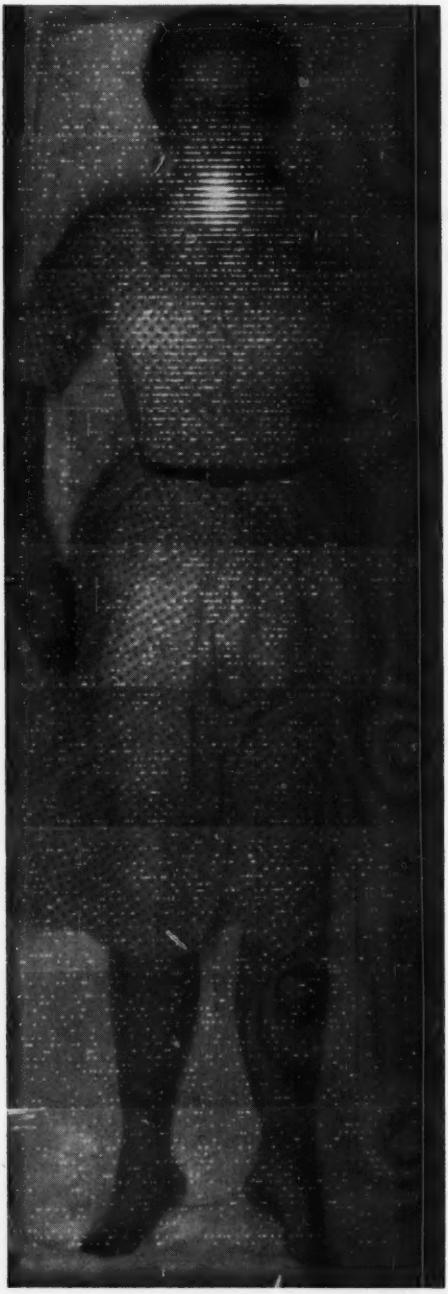

Fig. 2. Combined optical and gamma-ray images accurately display the site of I^{131} uptake.

tect any lesions that may take up the isotope. When the gamma-ray image shows an area that concentrates I^{131}, the site of the uptake should be located as accurately as possible. One method is to superimpose the gamma-ray image on an x-ray radiograph, as reported by West (1). The area of concentration of iodine is thereby located with respect to the x-ray anatomy of the patient. However, this procedure increases the radiation dose received. Therefore, we have built an apparatus that automatically superimposes an optical photograph of the patient on the gamma-ray image.

The gamma-ray scanner used for this purpose was built by one of the authors in 1952 (2). It employs ten scintillation counters mounted in a lead shield that moves over the patient. Each counter is connected through a scale-of-one circuit to a glow lamp which flashes with every count detected. As the counters move slowly over the patient, a moving image of the glow lamps is projected onto photographic film. The pattern of radioactivity in the subject is reproduced as a pattern of dots on the film. We have added a telephoto lens and mirror system to this apparatus which allows taking a photograph of the patient on the same film. Magnification and location of the photographic image are such that it coincides exactly with the size and location of the gamma-ray image.

The apparatus is shown in Fig. 1. The optical camera is located where it is easy to operate, and the two mirrors provide the necessary vertical view of the patient. Subject-to-camera distance is made as long as feasible, to reduce the distortion that would be caused if the camera were too near the patient. A 360-mm focal-length lens is used. To obtain pictures with the apparatus, a Polaroid-Land camera back containing the film is placed in position in the camera and an optical picture of the patient is taken. Then the camera back is placed in the glow-lamp box, where the gamma-ray image is recorded on the same film while the counters scan the subject. The film is developed rapidly by the Polaroid-Land process. Each scan covers an area 8 inches wide by 30 inches long. Head-to-toe pictures are produced by combining the images from nine adjacent scans.

Figure 2 shows an example of the distribution of I^{131} in a patient. The iodine has concentrated almost entirely in the thyroid region, where some thyroid tissue was left after an operation. The optical apparatus has been in use for more than a year and we believe it has significantly improved the diagnostic value of the whole-body scanner.

ACKNOWLEDGMENT

The authors wish to thank Dr. D. J. Rosenthal for his assistance during this study.

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JOURNAL OF NUCLEAR MEDICINE 2:102, 1961

The Pancreas Specificity of Se^{75}-Selenomethionine[1,2]

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Buffalo

INTRODUCTION

Carcinoma of the pancreas is responsible for the death of approximately 7000 persons each year in the United States. During the past 20 years surgical techniques for the resection of carcinoma of the pancreas have been perfected; however, few cases are diagnosed sufficiently early to be suitable candidates for operation. Radioisotope scanning techniques often provide a convenient method for the visualization of normal and abnormal tissues when x-ray procedures are unsatisfactory. Recent improvements in instrumentation permit the visualization of small, deep-seated lesions (1, 2). The search for suitable radioactive (3, 4, 5) pancreas specific agents has been notably unproductive. This paper presents animal data on a new agent, Se^{75}-selenomethionine, which has a high pancreas specificity and may prove suitable for radioisotope scanning of the human pancreas.

PREPARATION OF SE^{75}-SELENOMETHIONINE

The Se^{75}-selenomethionine used in these experiments was prepared by biosynthesis. Yeast was grown on a low sulfur medium containing high specific activity Se^{75} as selenite. Following extraction with ether and hot trichloracetic acid, the yeast residue was hydrolyzed with hydrochloric acid. The resulting amino acid mixture was separated by column chromatography. The overall yield was about 10 per cent.

A detailed protocol of this preparation has been published elsewhere (6).

PANCREAS SPECIFICITY OF AMINO ACIDS

There have been many reports of high amino acid concentrations in the pancreas shortly after the intravenous administration of C^{14} and S^{35} labeled amino acids (7, 8, 9). We have confirmed these reports in our laboratory. All amino acids tested show a high localization in pancreas 1 hour after administration. The most active compound tested was DL-Tryptophane-C^{14}. Over 12 per cent of the injected dose was found in the rat pancreas after one hour (Table 1).

1. From the Department of Nuclear Medicine, Roswell Park Memorial Institute Buffalo.
2. Supported by United States Public Health Service Grant #CS-9600.

TABLE 1. DISTRIBUTION OF TRYPTOPHANE DERIVATIVES IN RATS 1 HOUR AFTER I. V. ADMINISTRATION

Compound	*Per Cent Dose in Total Organ*				
	Pancreas	*Liver*	*Kidney*	*Spleen*	*Blood*[a]
Tryptophane-C^{14}	12.5	11.1	3.10	.82	5.2
N-Iodo acetyl tryptophane-I^{131}	.27	3.54	.80	.20	12.0
5-OH Tryptophane-C^{14}	1.28	1.54	1.44	.20	2.6

[a] Blood value calculated for 7% of body weight.

TABLE 2. DISTRIBUTION OF SE^{75}—SELENOMETHIONINE IN DOGS 2 HOURS AFTER ADMINISTRATION

Route	*Treatment*	*Per Cent Dose*[a]				
		Pancreas	*Liver*	*Spleen*	*Kidney*	*Blood*[b]
I. V.	Injected 2 hours after feeding	5.0 (.25)	14.8 (.036)	.77 (.021)	2.2 (.034)	8.4 (.011)
I. V.	Injected 30 minutes before feeding	4.5 (.14)	18.6 (.023)	.33 (.009)	2.2 (.020)	7.1 (.006)
Sub Q	Injected 1 hour after feeding	6.4 (.19)	11.3 (.020)	.33 (.008)	1.4 (.016)	4.3 (.005)
Sub Q	Injected 30 minutes before feeding	7.6 (.17)	10.9 (.020)	.64 (.014)	2.0 (.019)	6.3 (.007)
I. V.	Starved 24 hours	7.4 (.23)	17.3 (.045)	.87 (.008)	2.2 (.037)	9.2 (.011)
Sub Q	Starved 24 hours	6.3 (.34)	11.9 (.053)	.34 (.008)	1.6 (.037)	7.2 (.011)
Oral	Starved 24 hours	5.7 (.15)	21.4 (.040)	.36 (.007)	2.9 (.020)	4.1 (.004)

[a] Upper values % dose total organ. Lower values (in parentheses) % dose per gram.
[b] Total blood value calculated for 7% of body weight.

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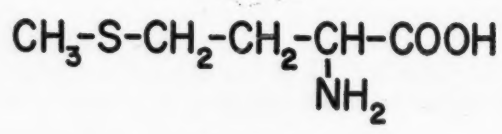
The high degree of localization of amino acids in the pancreas is probably related to the synthesis of the pancreatic enzymes. The very rapid utilization and destruction of the digestive enzymes in comparison with other body proteins requires a rapid rate of synthesis by the pancreas and explains the high amino acid uptake.

Unfortunately none of the elements in the structure of amino acids (C, H, N, O, & S) have gamma-emitting isotopes with half-lives longer than a few minutes. Since external measurements can only be done with gamma radiation, an amino acid derivative or analog containing such an isotope must be used. Our first attempts were concerned with derivatives of tryptophane. Table 1 gives the distribution data for two tryptophane derivatives. 5-OH-tryptophane was available and was studied to determine the effect of small ring substitutions and the n-iodo-acetyl derivative was prepared to study the effect of substitution at the NH_2 group. The data in Table 1 indicate that even small modifications of the tryptophane molecule destroy the pancreas localizing ability. Mono-iodotyrosine also failed to show any pancreas specificity.

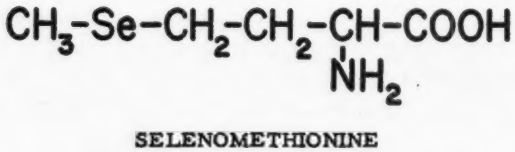
DISTRIBUTION OF SE^{75}-SELENOMETHIONINE IN DOGS

It appeared, therefore, that the tagging of the amino acid would have to involve changes less extensive than the addition of even a small external group. The chemical similarity of selenium and sulfur suggested that the selenium analog of methionine (Fig. 1) might resemble methionine closely enough to take its place in protein synthesis. The substitution of selenium for sulfur had the additional attraction of the availability of an isotope of selenium, Se^{75} (half-life, 128 days; principal δ ray, .27 MEV) which is suitable for scanning.

The distribution of this compound has been studied in more than 30 dogs, using different routes of administration, time of feeding, etc. In each case, there



METHIONINE



SELENOMETHIONINE

Fig. 1. Chemical Structure of Methionine and Selenomethionine.

was significant localization in the pancreas. The highest quantities are found 1-2 hours after administration. Table 2 shows typical distribution data at 2 hours. The quantity found in the pancreas is about 6 per cent, which is approximately the amount found after the injection of methionine-C^{14}.

The concentration (per cent dose per gram) of radioactivity in the pancreas is as much as eight or nine times as high as the liver when the selenomethionine is given just before or just after feeding. This differential uptake is probably sufficient for pancreas scanning. Starvation seems to elevate the amount found in the liver, reducing the pancreas to liver ratio in these animals. Concentrations found in the other viscera and in blood are lower than in liver.

The route of administration seems to have no large effect on either the pancreas or liver values but subcutaneous injection does give slightly better localization.

SUMMARY

Se^{75}-selenomethionine has been prepared. This compound shows the pancreas specificity characteristic of amino acids. About 6 per cent of the dose can be found in the pancreas 2 hours after administration and the concentration in the pancreas is as high as eight or nine times that found in the liver. This distribution data and the radiation characteristics of Se^{75} suggest that Se^{75}-selenomethionine might be useful for visualization of the pancreas by isotope scanning techniques.

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The Society of Nuclear Medicine
Eighth Annual Meeting
Hotel Penn-Sheraton
Pittsburgh, Pennsylvania

Scientific Program

WEDNESDAY, JUNE 14, 1961

9:00 A.M. Registration—Alcove in front of SKY ROOM
10:00 A.M. Joint Meeting of Board of Trustees and Executive Committee—ALLEGHENY ROOM
12:00 P.M. Executive Committee and Board of Trustees Luncheon—SKY ROOM
1:30 P.M. Joint Meeting of Board of Trustees and Executive Committee—ALLEGHENY ROOM

Instructional Session—URBAN ROOM

3:00 Radioisotopes in Microbiology and Immunology. (78)*
JOSEPH STERNBERG, Montreal.

3:30 Radiobiology. (80)
ROBERT L. STRAUBE, Lemont, Illinois.

4:00 Radiological Safety and Protection. (28)
THEODORE FIELDS, Hines, Illinois.

4:30 Radioautography, Principles and Procedures. (40)
DAVID L. JOFTES, Boston.

5:00 Demonstration in Radioautography.
DAVID L. JOFTES, Boston.

Joint Evening Meeting—Pittsburgh Society of Nuclear Medicine
Pittsburgh Roentgen Society —URBAN ROOM

Program Organized by Education Committee
The Society of Nuclear Medicine

8:00 Opening Remarks—JOSEPH STERNBERG, *Chairman*, Montreal.

8:15 On Being Well-Named: A Standard Nomenclature for Radioisotope Procedures. (43)
ERVIN KAPLAN, Hines, Illinois.†

8:45 Medical Qualifications for Nuclear Medicine. (25)†
LEE FARR, Upton, Long Island, New York.

9:15 The Future of Nuclear Medicine. (51)†
JOHN MCAFEE, Baltimore.

Number in parenthesis following each title in the Program refers to the corresponding abstract. The abstracts have been arranged numerically and have been published in the special convention issue of The Journal of Nuclear Medicine (April, 1961)

†*Each presentation will be discussed by invitation and from the floor.*

THURSDAY, JUNE 15, 1961

8:30 Registration—Alcove in front of SKY ROOM

Morning Session—URBAN ROOM

9:15 Formal Opening and Welcome—TITUS C. EVANS, President, The Society of Nuclear Medicine, State University of Iowa College of Medicine, Iowa City.

Chairman: TITUS C. EVANS, Ph.D., State University of Iowa College of Medicine, Iowa City.

9:30 Pancreas Visualization with Se^{75} Selenomethionine. (8)
MONTE BLAU and MERRILL A. BENDER, Buffalo.

9:50 Localization of Intracranial Lesions with the Saskatoon (Reid-Johns) Automatic Scanner. (16)
GEORGE A. B. COWAN, SYLVIA O. FEDORUK, JOSEPH G. STRATFORD, and KENNETH W. E. PAINE, Saskatoon, Canada.

10:10 A Study of the Effect of I^{131} Radiation on Cell Division in the Thyroid Using Tritiated Thymidine. (22)
BROWN M. DOBYNS and MARY ANN JENKINS, Cleveland.

10:30 Exhibit Break.

Chairman: HENRY JAFFE, M.D., Cedars of Lebanon Hospital, Los Angeles.

11:00 Pituitary Alpha Particle Irradiation. (47)
JOHN H. LAWRENCE, CORNELIUS A. TOBIAS, and JAMES L. BORN, Berkeley, California.

11:20 Pernasal Transsphenoidal Yttrium-90 Hypophysectomy. (57)
ROBERT D. MOSELEY, JR. and PAUL V. HARPER, JR., Chicago.

11:40 Present Status of I^{131}-Induced Hypometabolism As Treatment of Intractable Heart Disease. (9)
HERRMAN L. BLUMGART, Boston.

12:00 Lunch and Exhibit Viewing

Afternoon Session—URBAN ROOM

SECOND ANNUAL ADDRESS IN THE NUCLEAR PIONEER SERIES

2:00 *Presiding:* TITUS C. EVANS, Ph.D., Iowa City
Introduction and Presentation of Scroll: RICHARD E. PETERSON, M.D., Iowa City.
BECQUEREL-CURIE MEMORIAL LECTURE: GEORGE DE HEVESY, Ph.D., Dc.Sci., M.D., Guest Lecturer, Research Institute of Organic Chemistry, University of Stockholm, Stockholm, Sweden.

3:00 Exhibit Break
Chairman: RICHARD E. PETERSON, M.D., Veterans Administration Hospital, Iowa City.

3:30 An Improved Multicrystal Large Well Counter. (13)
BENEDICT CASSEN, Los Angeles.

3:50 A Simplified Method for Immuno-Assay of Human Serum Insulin Levels—Application to Clinical Studies. (54)
ROBERT C. MEADE, Milwaukee.

4:10 Some Applications of Radioactive Isotopes in Renal Function. (23)
R. DOMINGUEZ, Cleveland.

4:30 The Effect of Various Agents on the Removal of Radiostrontium from Man. (75)
HERTA SPENCER and JOSEPH SAMACHSON, New York.

4:50 Site of Binding of Cr^{51} to Hemoglobin. (64)
HOWARD A. PEARSON, Bethesda, Maryland.

FRIDAY, JUNE 16, 1961

Morning Sessions

SESSION 1—URBAN ROOM

Chairman: O. B. HUNTER, JR., M.D., Washington, D.C.

8:30 A Critical Evaluation of Isotopic Lipid Techniques to Measure Fat Absorption. (6)
DONALD BERKOWITZ, MILLARD W. CROLL, and BERNARD SHAPIRO, Philadelphia.

8:45 Estimation of Fat Absorption by Monitoring of Expired Radioactive Carbon Dioxide. (73)
A. D. SCHWABE, F. J. COZZETTO, S. M. MELLINKOFF, and L. R. BENNETT, Los Angeles.

9:00 Internal Dose in Humans. (35)
R. L. HAYES and W. R. BUTLER, JR., ORINS, Oak Ridge.

9:15 Biochemical Studies on the T-3 RBC Uptake. (67)
JOSEPH L. RABINOWITZ, Philadelphia.

9:30 The Influence of Protein Patterns on the Erythrocyte Uptake of I^{131} Triiodothyronine. (50)
GEORGE B. MCADAMS, Hartford, Connecticut.

9:45 Twelve Years Experience with 7000 REPS As the Therapeutic Dose for Thyrotoxicosis. (81)
WILLIAM C. SUTTON and HERBERT C. ALLEN, JR., Houston.

10:00 Exhibit Break

Chairman: JOHN F. SCHOLER, M.D., Palo Alto Medical Clinic, Palo Alto, California.

10:30 Thyroid Uptake of I^{132} Following Therapeutic Doses of I^{131}. (14)
RALPH R. CAVALIERI and E. RICHARD KING, Bethesda, Maryland.

10:45 Clinical Experience with I^{125}. (33)
PAUL V. HARPER, HAROLD ENDLICH, KATHERINE A. LATHROP, and WARREN SIEMENS, Chicago.

11:00 Use of Neutron Activation Analysis for Studying Stable Iodide Uptake by the Thyroid. (61)
WIL B. NELP, HENRY N. WAGNER, JR., and JAMES N. DOWLING, Bethesda, Maryland.

11:15 On the Mechanism of Action of Thyrotropin on the Thyroid. (66)
J. A. PITTMAN, B. H. WILLIAMS, and D. H. HAMNER, Birmingham, Alabama

11:30 Thyroid Function and Hepatic Injury by Cerium. (46)
GRANVIL C. KYKER, JOHN RAFTER, and FRED SNYDER, Oak Ridge.

11:45 Study of the Spermatogenesis in Man Using Radioactive Phosphorus (p^{32})—Establishment of a Spermatogenic Activity Test (SAT). (18)
P. CZERNIAK, Tel-Hashomer, Israel.

12:00 Lunch and Exhibit Viewing

SESSION 2—MONONGAHELA ROOM

Chairman: PAUL MEADOWS, M.D., Presbyterian Hospital, Pittsburgh.

8:30 "Blind End" Technique for Iridium-192 Removable Nylon Ribbon Interstitial Implants. (48)
LEONARD M. K. LIEGNER, New York.

8:45 Therapy of Malignant Serous Effusions with Radioyttrium (Y^{90}). (32)
JOSEPH GREENBERG and H. C. DUDLEY, New York.

9:00 Use of Intra-Abdominal Radioisotopes in the Treatment of Ovarian Carcinoma. (3)
IRVING M. ARIEL, New York

9:15 Intracavitary Radioactive Colloidal Gold—Results in 257 Patients. (70)
RAYMOND G. ROSE, Houston.

9:30 Human Hematological and Other Effects of Large Doses of S^{35} and Possibilities for Protection of the Bone Marrow. (2)
J. ROBERT ANDREWS, HAZEL P. GUMP, KIRKLAND C. BRACE, LOUIS V. AVIOLI, and HASKINS K. KASHIMA, Bethesda, Maryland.

9:45 Hematologic Events As Dosimeters in Total-Body Radiation. (52)
WILLIAM MCFARLAND and HOWARD A. PEARSON, Bethesda, Maryland.

10:00 Exhibit Break

Chairman: R. MURRAY CUNNINGHAM, M.D., Royal Victoria Hospital, Montreal.

10:30 The Effect of Total-Body Gamma Radiation on the Fibrinolytic System of Lung-Relationship to Hyaline Membrane Formation. (29)
WILLIAM H. FLEMING, JENO SZAKACS, and E. RICHARD KING, Bethesda, Maryland.

10:45 Distribution of Radioactivity at the Site of Localized and Proved Intracranial Lesions. (17)
GEORGE A. B. COWAN, SYLVIA O. FEDORUK, JOSEPH G. STRATFORD, and KENNETH W. E. PAINE, Saskatoon, Canada.

11:00 Measurement of Cerebral Circulation by External Collimation Following the Intravenous Injection of Radioisotope. (62)
W. H. OLENDORF, Los Angeles.

11:15 The Determination of Cerebral Circulation Time. (5)
ROBERT L. BELL and GEORGE J. HERTSCH, Brooklyn and New York.

11:30 Concomitant Radioisotopic and Radiography Cerebral Arteriography. (38)
JAMES JACKSON, BARNES WOODHALL, GEORGE J. BAYLIN, RONALD KRUEGER, and AARON P. SANDERS, Durham, North Carolina.

11:45 EDTA-Co "Gamma-Ray Carrier." (59)
WILLIAM G. MYERS, Columbus, Ohio.

12:00 Lunch and Exhibit Viewing

Afternoon Sessions

1:40-2:00 Business Meeting and Election of New Officers—URBAN ROOM

SESSION 1—URBAN ROOM

Chairman: JOSEPH GREENBERG, M.D., N. Y. Polyclinic Medical School, New York.

2:00 Radioiron Studies in the Investigation of Polycythemia Vera. (74)
W. JOHN SIMPSON and MARC C. BERTRAND, Toronto.

2:15 The Value of the Plasma Iron Turnover in the Differential Diagnosis of the Polycythemias. (85)
NANCY TELFER, NORMAN L. SCHIFFMAN, and FRANZ K. BAUER, Los Angeles.

2:30 Iron Absorption Using Fe^{59} and Low Background Whole Body Counter. (12)
JOSEPH S. BURKLE and WILLIAM MCFARLAND, Bethesda, Maryland.

2:45 Quantitation of Menstrual Blood Loss—Development of a Simple, Accurate Method. (84)
W. NEWLON TAUXE, Rochester, Minnesota.

3:00 Regulation of Red Cell Production by Erythropoietin. (87)
DONALD VAN DYKE and JOHN H. LAWRENCE, Berkeley, California.

3:15 Exhibit Break
Chairman: GRANVIL KYKER, Ph.D., ORINS Medical Division, Oak Ridge.

3:45 Value of Tagged Hemoglobin in Reticulo-Endothelial Studies. (30)
ELEMER R. GABRIELI, ALONZA JOHNSON, MANUEL SCHREIBER, PHILENA HECKERT, and ALICE ELLIOTT, Buffalo.

4:00 The Co^{60} Vitamin B_{12} Binding Capacity of Mature and Immature Leukocytes. (56)
LEO M. MEYER, EUGENE P. CRONKITE, ROBERT W. BERTCHER, INEZ F. MILLER, IRVING JONES, and CLAIRE W. MULZAC, Upton, Long Island, New York.

4:15 The Anemia of Leukemia (A Study of the Erythrokinetics of the Leukemias Using Iron-59 and Chromium-51). (10)
E. J. WALTER BOWIE, W. NEWLON TAUXE, J. M. STICKNEY, and JOSEPH M. KIELY, Rochester, Minnesota.

4:30 P^{32} Incorporation by Adenine Nucleotides As Affected by Some Psychochemical Agents. (7)
JOSEPH BERNSOHN and JAMES CUSTOD, Hines, Illinois.

4:45 Acid Quenching in Liquid Scintillation Assay of Tritium. (88)
ROGER VEATCH and I. GORDON FELS, Hines, Illinois.

SESSION 2—MONONGAHELA ROOM

1:40-2:00 Business Meeting and Election of New Officers—URBAN ROOM

Chairman: CHARLES HLAD, M.S., Veterans Administration Hospital, Denver.

2:00 Determination of the Specificity of Antibody Response to Endotoxin by Precipitation of Cr^{51}-Labeled Endotoxin. (45)
D. KOCH-WESER, Cleveland.

2:15 Validity of Measurement of Hepatic Blood Flow by Colloidal Clearance Methods. (68)
MOHAMED A. RAZZAK, HENRY N. WAGNER, JR., Baltimore.

2:30 The Effect of Endotoxin on Hepatic Blood Flow. (58)
JOHN M. MOSES, WILLIAM J. MACINTYRE, and DIETER KOCH-WESER, Cleveland.

2:45 The Clearance of Labeled Compounds As a Measurement of Hepatic Flow Versus Function. (49)
WILLIAM J. MACINTYRE, DIETER KOCH-WESER, JAMES H. CHRISTIE, and GODOFREDO GOMEZ CRESPO, Cleveland.

3:00 Colloidal Suspensions of Human Albumen I^{131} (Tracer Techniques for Estimating Functional Abnormalities of the Reticuloendothelial System [RES]). (82)
G. V. TAPLIN, E. K. DORE and D. E. JOHNSON, Torrance, California.

3:15 Exhibit Break

Chairman: WILLIAM J. MACINTYRE, Ph.D., Western Reserve University, Cleveland.

3:45 A Descriptive Analysis of Vascular Beds. (39)
JOSEPH M. JAMES, ALLEN M. LESAGE, G. S. EADIE, and W. GLENN YOUNG, Durham, North Carolina.

4:00 Evaluation of Tracer Methods for Estimating Coronary Blood Flow. (41)
D. E. JOHNSON, C. K. LIU, G. V. TAPLIN, and E. K. DORE, Torrance, California.

4:15 Myocardial Blood Flow of Patients Submitted to Vascular Surgery. (42)
PHILIP C. JOHNSON, JR., Houston.

4:30 Detection of the Small Left to Right Cardiac Shunt with Methyl Iodide-131. (53)
FABER F. MCMULLEN, JR., WILLIAM C. SUTTON, HERBERT C. ALLEN, and HUGH H. HANSON, Houston.

4:45 Xenon-133 Studies of Pulmonary Physiology. (4)
W. C. BALL, JR., P. B. STEWART, L. G. S. NEWSHAM, and D. V. BATES, Montreal.

SATURDAY, JUNE 17, 1961

Morning Sessions

SESSION 1—URBAN ROOM

Chairman: GEORGE V. TAPLIN, M.D., University of California, Los Angeles.

8:30 Diagnostic Applications of Ca^{47} and Sr^{85} to Tumors Involving Bone. (15)
K. R. COREY, P. KENNY, E. GREENBERG, J. S. LAUGHLIN, and B. S. RAY, New York.

8:45 Strontium-85 As a Tracer for Calcium in Man. (72)
JOSEPH SAMACHSON and HERTA SPENCER, New York.

9:00 The Binding of I^{131} Labeled Contrast Media by Human Serum. (26)
RICHARD S. FARR, ELLIOTT C. LASSER, and GERALD P. RODNAN, Pittsburgh.

9:15 Carrier Dose Effects Upon Blood Disappearance Rates of the I^{131}-Iodopyracet Radioisotope Renogram in Rabbits. (55)
O. M. MEREDITH, JANE POST, and JOHN HOLMES, Los Angeles.

9:30 Renal Blood Flow Measurement from Blood Clearance of a Single Injection of Hipputope. (31)
FRANK STOREY GOTT, WALTER H. PRITCHARD, WILLIAM R. YOUNG, and WILLIAM J. MACINTYRE, Cleveland.

9:45 Exhibit Break

Chairman: DONALEE TABERN, Ph.D., Highland Park Hospital Foundation, Highland Park, Illinois.

10:15 Radiohippuran in the Determination of Effective Renal Plasma Flow. (11)
MAHLON K. BURBANK, W. NEWLON TAUXE, FRANK T. MAHER, and JAMES C. HUNT, Rochester, Minnesota.

10:30 Radioisotope Renograms with 2, 6-Diiodosulfanilate-I^{131} As a Test Agent. (89)
CHESTER C. WINTER and WILLIAM G. MYERS, Columbus, Ohio.

10:45 Analysis of the Radioactive Renogram Curve by an In Vitro Experiment. (65)
FELIX J. PIRCHER, AUDREY V. WEGST, and VERNON N. DODSON, Ann Arbor.

11:00 The Radiorenocystogram in Upper Urinary Tract Infections. (24)
E. K. Dore, D. E. Johnson, and G. V. Talpin, Torrance, California.

11:15 Renal Scintigrams in the Diagnosis of Renal Vascular Disease. (36)
Thomas P. Haynie, Mohamed M. Nofal, Edward A. Carr, Jr., and William H. Beierwaltes, Ann Arbor.

SESSION 2—MONONGAHELA ROOM

Chairman: Monte Blau, Ph.D., Roswell Park Memorial Institute, Buffalo.

8:30 Evaluation of Two Compartment Systems by Continuous Gamma Monitoring of a Dialysis-Perfusion Device. (44)
Ervin Kaplan and John J. Imarisio, Hines, Illinois.

8:45 Medical Applications of the Personal Radiation Monitor. (21)
R. H. Dilworth and C. J. Borkowski, ORNL, Oak Ridge.

9:00 Scanning with a Compact Transistorized Scintillation Detector and Polaroid Recording. (27)
Theodore Fields, Glenn Clayton, Joseph Kenski, and Ervin Kaplan, Hines, Illinois.

9:15 An Improved Display Method for Scintiscanning. (37)
Fred C. Heagy, Arthur Vaart, and John C. F. MacDonald, London, Ontario, Canada.

9:30 Criteria for Evaluating Collimators Used In Vivo Distribution Studies with Radioisotopes. (20)
W. C. Dewey, and W. K. Sinclair, Houston.

9:45 Exhibit Break

Chairman: Herbert C. Allen, M.D., Hermann Hospital, Houston.

10:15 An Automatic Electronic Method of Analyzing Scan Records. (34)
Craig Harris, P. R. Bell, and J. E. Francis, Jr., Oak Ridge.

10:30 Estimation of Liver Size by Multiple Cut-Off Scanning Techniques. (90)
Rauf Yagan, W. J. MacIntyre, W. B. Chamberlin, and J. H. Christie, Cleveland.

10:45 The Topographic Distribution of Liver Metastases. Its Relation to Surgical and Isotope Diagnosis. (63)
Ahcen Ozarda and John Pickren, Baltimore.

11:00 Scintillographic Follow-up of Amoebic Abscess and Hydatid Cysts of the Liver. (19)
P. Czerniak, E. Lubin, M. Djaldetti, and A. De Vries, Petah Tiqua and Tel-Hashomer, Israel.

11:15 The Measurement of Total Body Potassium in Man and Its Relation to Gross Body Composition. (69)
Alexander P. Remenchik and Charles E. Miller, Hines, Illinois.

Papers to be Read by Title

The Private Practice of Nuclear Medicine As a Speciality. (1)
HERBERT C. ALLEN, Houston.

Radioiodine-125 for Standardization of Low-Energy Photon Emitters. (60)
WILLIAM G. MYERS AND PRENTISS M. DETTMAN, Columbus, Ohio.

Review of Studies of the Removal of Fission Products from Man. (71)
BETTY ROSOFF AND HERTA SPENCER, New York.

Comparison of the Suppressive Effects of Triiodothyronine and Potassium Iodide. (76)
MAXWELL SPRING, Bronx, New York.

The Use of Triiodo-Thyroproprionic Acid (Triopron) in the Therapy of Hypothyroidism. (77)
MAXWELL SPRING, Bronx, New York.

The "In Vitro" Uptake of C^{14}-Labeled Cholesterol by Red Blood Cells. (79)
JOSEPH STERNBERG, Montreal.

Heat Denatured Colloidal Suspension of RISA. Simplified Method of Preparation. (83)
G. V. TAPLIN, M. L. GRISWOLD, AND E. K. DORE, Torrance, California.

A Course in Radioisotopes Presented for Pharmacy and Medical Residents and Technicians. (86)
MANUEL TUBIS, Los Angeles.

Implant Dosimetry. (91)
C. G. AMATO, S. J. MALSKY, B. ROSWIT, AND V. P. BOND, Upton, Long Island, New York.

Medical Reactor Technology. (92)
C. G. AMATO, S. J. MALSKY, B. ROSWIT, AND V. P. BOND, Upton, Long Island, New York.

Medical Reactor Neutron Spectroscopy. (93)
C. G. AMATO, Upton, Long Island, New York.

Determination of Liver Function with I^{131} Rose Bengal. (94)
GEORGE J. CARROLL, Suffolk, Virginia.

Alterations in Thyroid Function Associated with Cancer. (95)
SIDNEY RUBENFELD, D. JOSEPH PASTORELLE, AND CARL J. COLLICA, Bellevue Hospital, New York.

Abstracts

1. ***The Private Practice of Nuclear Medicine as a Specialty.*** **Herbert C. Allen, Jr. (Texas Medical Center, Houston)**

Indications for and importance of the establishment in a community of a Nuclear Medicine Laboratory designed exclusively for clinical and laboratory diagnostic studies in association with a private practice devoted exclusively to Nuclear Medicine are presented.

The complications associated with such an endeavor will be reviewed in detail. Experience gained in the first year of the private practice of atomic medicine will be discussed. The morbidity and mortality rate of Nuclear Medicine as a separate and distinct speciality will be projected. Various concepts of the ultimate fate and survival of the speciality of Nuclear Medicine will be explored including the vertical, horizontal and pyramidal theories. The importance of the symbiotic relationship with industry active in the atomic energy field for the successful operation of such an enterprise are emphasized.

The selection of the location of the physical facility, the equipment and personnel required are presented.

2. ***Human Hematological and Other Effects of Large Doses of S^{35}.*** **J. Robert Andrews, Hazel P. Gump, Kirkland C. Brace, Louis V. Avioli, and Haskins K. Kashima (Radiation Therapy Service, Radiation Branch, National Cancer Institute, National Institutes of Health, Bethesda)**

Large doses of inorganic S^{35} have been given to patients with inoperable chondrosarcoma and the distribution of S^{35} in tumor and normal tissues has been studied. The immediate complication of a large dose of S^{35} intravenously administered is hematologic depression. The effects of arterial constriction and refrigeration of the limbs during the administration of S^{35} has been studied in one patient and the differences in blood serum levels and urinary excretion of S^{35} under these conditions are described.

3. ***Use of Intra-Abdominal Radioisotopes in the Treatment of Ovarian Carcinoma.*** **Irving M. Ariel (Pack Medical Group, New York)**

Intra-abdominal radioisotopes have been used in forty patients with carcinoma of the ovary. Three groups of patients were treated: (1) those receiving radioisotopes after surgery as a prophylaxis against the development of metastases; (2) patients with disseminated metastases in the abdominal cavity but in whom no ascites was present; (3) patients with ovarian carcinoma and ascites.

The radioisotopes used have uniformly been a combination of an isotope with a short half-life (radioactive gold or radioactive yttrium) and an isotope with a longer half-life (radioactive chromium phosphate).

The results are most encouraging: 75 per cent of the patients with disseminated ovarian carcinoma are benefited. In four patients with extensive carcinomatosis, subsequent laparotomy failed to reveal the presence of cancer. One woman, age 23, with extensive intra-abdominal metastases including massive infiltration of the omentum, was given 75 millicuries of radioactive gold and 20 millicuries of radioactive chromic phosphate. Four months later she was given an additional 20 millicuries of radioactive chromic phosphate intra-abdominally. It was later discovered that she was one month pregnant when the chromic phosphate was given. She was delivered by Cesarian section. The child was normal in every respect, and at the time of the exploration she was found to be completely free from cancer.

4. ***Xenon-133 Studies of Pulmonary Physiology.*** **W. C. Ball, Jr., P. B. Stewart, L. G. S. Newsham, and D. V. Bates (Department of Medicine and Radiology of the Royal Victoria Hospital and McGill University, Montreal, Canada)**

Xenon-133 is a readily available inert radioactive gas which emits low energy gamma ray and is thus suitable for *in vivo* studies of respiration. An array of collimated scintillation counters is placed over the posterior chest wall and the count rate from selected areas of the lung are recorded on a multiple channel tape recorder while the subject inhales a known concentration of radioactive gas from a spirometer. These count rates are then played back through ratemeters, to be recorded on charts. The function of different regions of the lungs can then be inferred from the results. By injecting a known quantity of the Xenon-133 in solution into the blood stream and observing its appearance in the lung a determination can be made of the perfusion in various regions.

5. ***The Determination of Cerebral Circulation Time.*** **Robert L. Bell and George J. Hertsch (State University of New York and Kings County Hospital, Brooklyn; Dept. of Hospitals, City of New York, Francis Delafield Hospital, New York)**

The technique described permits the accurate semi-closed measurement of transit times between the internal carotid artery and the outflow of both the deep and superficial venous circulation of the brain. The tracer slug is either RISA or Neohydrin Hg^{203}. The system incorporates highly directional probes and a non-destructive tape recording and playback device. The playback record may be processed to enhance the display of data. Several illustrations of normal and delayed transit times are presented and correlated with routine angiographic studies.

6. ***A Critical Evaluation of Isotopic Lipid Technics to Measure Fat Absorption.*** **Donald Berkowitz, Millard W. Croll, and Bernard Shapiro (Albert Einstein Medical Center, and Hahnemann Medical College, Philadelphia)**

During the past several years radioactive labelled triolein and oleic acid have been used with increasingly more popularity to study problems concerned with fat absorption.

Although earlier data appeared to indicate that these simplified isotopic technics could supplant the older and more difficult chemical balance procedures, continuing experiences have demonstrated that certain limitations to their use exist, and have made it necessary to more clearly define the specific criteria for the interpretation of their results.

Low blood radioactivity values do not necessarily indicate malabsorption but rather may result from delayed gastric emptying. On the other hand, normal blood radioactivity concentration may occasionally be present even in the presence of impaired absorption. Fecal radioactivity analyses in these cases constitute the deciding factors and accordingly should be done routinely in each case.

Another error may possibly result when a capsule test meal containing 0.5 to 1 ml of the tracer fat is used alone without an accompanying 50 - 100 ml of carrier fat. In an occasional patient with definite malabsorption the smaller amount of tagged fat may be completely absorbed. However when the larger volume is ingested, increased stool with decreased blood radioactivity levels are readily apparent.

Typical case records to demonstrate these points are described.

7. *P^{32} Incorporation Into Nucleotides.* **JOSEPH BERNSOHN and JAMES T. CUSTOD (Neuropsychiatric Research Laboratory, Veterans Administration Hospital, Hines, Illinois)**

To study the mechanism of action of psychogenic drugs on phosphorylation systems, the effect of a psychic energizer, phenyl isopropyl hydrazine (Catron) and a tranquillizer, chlorpromazine, on the incorporation of P^{32} into brain nucleotides, phosphocreatine, DPN, and inorganic phosphate was determined. The animals were injected with 2.5 mg/kg Catron and 10 mg/kg chlorpromazine i.p. over a period of 15-40 days. At the end of the experimental period, 100 microcuries of P^{32} was injected into the tail vein and the animals sacrificed by immersion in liquid nitrogen. The compounds were separated on a Dowex-1-formate column and P^{32} activity was measured in a Tri-Carb Scintillation Counter. From the results obtained it is evident that changes in phosphorylation mechanism result from administration of these drugs. Chlorpromazine may act by inhibiting active transport of phosphate across the blood brain barrier, while the increase in the specific activity of ATP after Catron administration may indicate a more rapid phosphate turnover in this phosphorylating system. The change in specific activity of phosphocreatine is more difficult to interpret.

8. *Pancreas Visualization with Se^{75} Selenomethionine.* **MONTE BLAU and MERRILL A. BENDER (Department of Nuclear Medicine, Roswell Park Memorial Institute, Buffalo)**

Amino acids show a high degree of localization in the pancreas during the first few hours after administration. This specificity is probably related to the synthesis of the digestive enzymes. Since none of the elements in the structure of amino acids (C, H, N, O, and S) have suitable gamma emitting isotopes, they cannot be used for scanning. Several I^{131} derivatives of amino acids were prepared and tested, but the pancreas localizing property of the original amino acid was lost in every case.

The selenium analog of methionine (with Se^{75} substituted for sulfur in the amino acid structure) was prepared by yeast biosynthesis. This compound was found to have a pancreas specificity equal to that of the natural amino acid. One hour after administration, up to 6 or 7% of the selenomethionine was found in the dog pancreas with the concentrations (% dose/gram) 8 or 9 times as high as the liver. Scans of these dogs show very satisfactory visualization of the pancreas. The externally measured uptake of this compound may prove useful as a pancreatic function test.

9. *Present Status of I^{131}-Induced Hypometabolism as Treatment of Intractable Heart Disease.* **HERRMAN L. BLUMGART, (Beth Israel Hospital, Boston)**

A recent survey of 2000 cases of intractable heart disease treated with I^{131}-ablation of the thyroid in over 100 clinics will be discussed. The consolidated results of the questionnaire survey will be presented in terms of types of cases treated, and evaluation of responses to the hypometabolic state. More detailed observations will be included on a large personal series of cases followed since 1947. Indications and contra-indications for this mode of treatment will be reviewed in terms of experience accumulated in the past 5 years.

10. *The Anemia of Leukemia—A Study of the Erythrokinetics of the Leukemias Using Iron-59 and Chromium-51.* **E. J. WALTER BOWIE, W. NEWLON TAUXE, J. M. STICKNEY, and JOSEPH M. KIELY (Mayo Foundation and Mayo Clinic, Rochester, Minnesota)**

Conflicting ideas regarding the pathogenesis of anemia in leukemia have been reported. In the present study erythrocyte production and destruction as well as gastrointestinal blood

loss were quantitated concurrently by the use of radioisotopes of iron and chromium. In addititon, external scintillation counting showed uptake of radioiron by marrow, liver, and spleen.

The results of the study support the view that anemia occurs in acute leukemia (eight patients) because the bone marrow is unable to compensate for the increased destruction of red blood cells. Blood loss from the gastrointestinal tract was not a significant factor. In two of the patients with acute leukemia, in vivo and postmortem studies gave evidence of a primary deposition of iron in the liver. After remission was produced with an antimetabolite agent, normal erythrokinetics were restored in one patient with acute leukemia.

In two of three patients with chronic granulocytic leukemia, evidence of impaired erythropoiesis was found. Plasma volumes were high in these patients, indicating hemodilution as a factor in the anemia.

No abnormality was found in the radioiron and radiochromium kinetics of three patients with chronic lymphocytic leukemia, two of whom were not anemic.

11. *Radiohippuran in the Determination of Effective Renal Plasma Flow.* MAHLON K. BURBANK, W. NEWLON TAUXE, FRANK T. MAHER, and JAMES C. HUNT (Mayo Clinic and Mayo Foundation, Rochester, Minnesota)

Because of the increased use of renal blood flow measurements, a method of using radioiodinated sodium orthoiodohippurate (Hippuran) was devised in an attempt to replace cumbersome chemical analysis in these determinations. It had been shown by previous investigations that inactive Hippuran had the same renal clearance as PAH, used ordinarily in such studies. A series of effective renal plasma determinations were done simultaneously with PAH and Hippuran in hypertensive patients. It was found that the ERPF derived from Hippuran averaged 12.9% lower than that derived from PAH in a series of 70 paired determinations. The possible causes of this difference between PAH and Hippuran clearance investigated and the quantities of free radioidide in the reagent were found to be the important element.

Each lot of Hippuran was analyzed to determine the amount of free iodine present. The study was then divided into four parts depending on the free I^{131} content found in the lots of Hippuran used. In the group with more than 5% free iodide, the Hippuran clearance was 20.4% lower than the PAH cleared; with 3.5 to 5%, 13.4% lower; with 2 to 3.5%, 9.9% lower; and with less than 2% free iodide, 9.2% lower. This showed that the amount of free iodide in the solution was critical and that the use of radioiodide free Hippuran solution should result in clearance equal to the PAH clearance. This method, while submitting the patient to minimal radiation (less than 3 millirad to the blood), has obvious advantages over standard chemical analysis in determining renal plasma flow.

12. *Iron Absorption Using Fe^{59} and Low Background Whole Body Counter.* JOSEPH S. BURKLE, CAPTAIN, MC, USN and WILLIAM MCFARLAND, CDR, MC, USN (Department of Nuclear Medicine, U. S. Naval Hospital, Bethesda)

Absorption of iron from the gastrointestinal tract was studied by a new and simple method. Two low background whole body counters in steel rooms are available. One room contains a 4 x 8 inch thallium-activated sodium iodide detector. This furnishes pulses via three multiplying phototubes and a pre-amplifier to a 256 channel analyzer. The other room has three 18 x 18 x 6 inch plastic blocks which furnish pulses to three 16 inch multiplying phototubes and four single channel analyzers.

The low dose of Fe^{59} (0.5–2.5 μc) and ease of performance of the test permitted repeated tests in the same patient. Since stool and blood collections were eliminated, there was less dependence on patient cooperation. The evaluation of children was, therefore, feasible. The results of normal and a series of abnormal patients are presented.

13. *An Improved Multicrystal Large Well Counter.* **BENEDICT CASSEN (Laboratory of Nuclear Medicine and Radiation Biology of the Department of Biophysics and Nuclear Medicine, School of Medicine, University of California, Los Angeles)**

An improved multicrystal sodium iodide scintillation well high counter has been constructed and tested. It can measure with very high efficiency in as much as 100 ml of fluid, tissue, or other objects, gamma activity at very low levels. For example, it can measure reasonably accurately with 256,000 counts at twice background, 0.00002 microcuries of I^{131} in 100 ml of urine or blood, with an absolute counting efficiency of about 85 per cent. The absolute counting efficiency is very good for Co^{60} and Fe^{59}. The earlier problems of drift and lack of stability appear to have been solved.

In the improved counter a cylindrical lucite box with a well-space built into it is filled as compactly as possible with relatively inexpensive pieces of sodium iodide crystals, roughly 2 cm cubes. The voids are filled with a light silicone oil. Two photomultipliers are placed in opposition against the flat ends of the cylindrical container. The container is packed around with a thin layer of dry alpha-aluminum oxide inside of a loose fitting metal container. The whole assembly is surrounded by more than two inches of lead.

As there is no light absorption associated with reflections and refractions at the crystal-fluid interfaces, the counter has some spectrometric resolution. There seems to be no essential limitation to building larger volume well counters using this principle. The average thickness of crystal space around the well does not have to be more than about two to three inches for efficient absorption and counting of most gamma emitters.

14. *Thyroid Uptake of I^{132} Following Therapeutic Doses of I^{131}.* **RALPH R. CAVALIERI, Lt., MC, USNR, and E. RICHARD KING, CAPTAIN, MC, USN (Department of Nuclear Medicine, U. S. Naval Hospital, Bethesda)**

The short-lived isotope I^{132} ($T_{½}$ 2.3 hours) offers several advantages over I^{131} in clinical investigations of thyroid function. The radiation exposure to the patient is significantly lower in the case of I^{132} allowing studies to be repeated in the same individual. Because of its higher energy gamma rays, I^{132} can be detected *in vivo* in the presence of considerable I^{131} activity, even therapeutic doses.

One and two-hour thyroid uptake measurements, neck-thigh ratio and thyroid clearance studies were done on normals, and hyperthyroid patients, before and after various forms of therapy.

Among patients under treatment with thiourea-type drugs, effectiveness of thyroid blockade was estimated and correlated with clinical response. This method allows one to gauge the adequacy of anti-thyroid medication without interruption of the drug and with low radiation exposure.

Thyroid uptake was measured directly in patients soon after therapeutic doses of I^{131} by giving larger tracer doses of I^{132} (100-300 microcuries) and by using a pulse height analyzer to eliminate most of the I^{131} counts. Details of the method will be described. Preliminary results in patients given single therapeutic doses of I^{131} (4 to 6 millicuries) for diffuse (toxic) goiter indicate that thyroid uptake and clearance return to normal by the eighth day after the therapy. Thiocyanate failed to release trapped I^{132} indicating that organification keeps pace with iodide trapping in such glands.

15. *Diagnostic Applications of Ca^{47} and Sr^{85} to Tumors Involving Bone.* **K. R. COREY, P. KENNY, E. GREENBERG, J. S. LAUGHLIN, and B. S. RAY (The Memorial Sloan-Kettering Cancer Center and The New York Hospital, New York)**

This report describes some diagnostic applications of a scanner designed for radioisotope studies of bone lesions. Data have been presented previously to show that active bone

metastases or primary tumors (whether healing or progressive and whether osteolytic or osteoblastic) concentrated Ca^{47} to a greater extent than corresponding uninvolved bone. The rate of accretion was found to be high in patients with active lesions and normal in those with arrested lesions. In the patients with high accretion rates and high Ca^{47} uptakes in lesions, lower uptakes than normal were found in healthy bones such as tibia and patella.

Results are reported on two patients after tracer doses of Ca^{47} and Sr^{85}. Both of these had mastectomy four years earlier. At the time of study they had pain but no known metastases. Elevated levels of radioactivity were observed in the areas of pain. Follow-up has so far resulted in the finding of bone metastases in two of these areas. These findings, the instrumentation, counting techniques, and implications of this method are discussed.

16. *Localization of Intracranial Lesions with the Saskatoon (Reid-Jones) Automatic Scanner.* **GEORGE A. B. COWAN, SYLVIA O. FEDORUK, JOSEPH G. STRATFORD, and KENNETH W. E. PAINE (Saskatoon Cancer Clinic and Departments of Therapeutic Radiology and Neurosurgery, University Hospital, Saskatoon, Saskatchewan, Canada)**

In the past five years, some 900 brain scans have been done, using the automatic scanner originally described by Reid and Johns. It has been modified to the extent that longer crystals (3″ by 1″) have been substituted in the simple, open-ended, ¾″ diameter collimators, so that an 'ideal' counting rate of approximately 600 per minute is obtained at 24 hours with only 200 microcuries of RISA. Both halves of the head are now scanned simultaneously in nine, instead of the original eight sagittal arcs, and the procedure is completed in roughly 30 minutes.

The most accurate localizations occur with lesions lying close to the midline. Although some 10% of proven lesions have been missed, approximately 90% correlation with other established investigative procedures is considered adequate reason for accepting the method as a screening procedure for tumor suspects and in the follow-up of proven brain tumors.

17. *Distribution of Radioactivity at the Site of Localized and Proved Intracranial Lesions.* **GEORGE A. B. COWAN, SYLVIA O. FEDORUK, JOSEPH G. STRATFORD, and KENNETH W. E. PAINE (Saskatoon Cancer Clinic and Departments of Therapeutic Radiology and Neurosurgery, University Hospital, Saskatoon, Saskatchewan, Canada)**

Although it is generally accepted that cystic tumors are not localizable, it is our experience that the opposite applies and that cystic astrocytomas may, in fact be localized and, indeed, that the cystic component may be strongly radioactive.

Evidence is presented of the radioactivity of some such cystic lesions and of a subdural hematoma (the latter localized with both Neohydrin–Hg^{203}, and RISA).

In view of the diversity of types of lesion which have been localized and the proof of radioactivity of cystic astrocytomas, a simple theory is presented which should be of interest to those engaged in the study of the 'blood-brain barrier'.

18. *Study of the Spermatogenesis in Man Using Radioactive Phosphorus (P^{32}). Establishment of a Spermatogenic Activity Test (SAT).* **P. CZERNIAK (Radium and Isotopes Institute, Tel-Hashomer Government Hospital, Tel-Hashomer, Israel)**

Approximately 85% of the phosphorus entering the human body is utilized in the synthesis of bone-salts; some of the phosphorus is excreted and the rest enters into biosynthesis with carbohydrates, lipids, proteins, ferments and enzymes. There is a big demand for phosphorus

for biosynthesis in tissues with active mitosis. In the fertile testis there is abundant mitosis. In the inactive one there is little mitotic activity and the phosphorus is not utilized.

We administered P^{32} to 82 men (29 fertile and the others sterile) and traced the P^{32}:

A) With a Geiger counter (mica window, 2.2 mg/cm^2) we measured the radiation emerging from the testes and compared this with that from other areas of the body. We obtained testicular uptake curves, characteristic of the various states of spermatogenic activity.

B) We measured the P^{32} in a testicular phantom and calculated from this the amount taken up by the testis examined (range, 0.05% to 0.003%). The biological half-life ranged from 6 to 15 days.

C) The P^{32} is excreted in the semen (in the form of LP, DNA, RNA, ASP). By means of a radiochemical technique we were able to separate the P^{32} and to measure it quantitatively (a 10^{-6} part of the amount injected).

All the patients underwent a clinical and laboratory investigation. In 18 cases we were able to examine the testes histologically.

The results of the investigations can be categorized as a Spermatogenic Activity Test (SAT). It may be positive, negative, or infantile. In practice it appears sufficient to observe the testicular uptake curve. The other investigations are performed for purposes of research and control. The performance of the SAT requires the injection I.V. in a forearm of 1 microcurie of P^{32} per 5-7 kilo body weight. Dosimetric calculations have shown that in this way each testis receives from 90 to 120 millirep of ionizing radiation.

SAT is not intended for screening. The indications for its performance may be for clinical, therapeutic, legal, or research purposes.

19. *Scintillographic Follow-up of Amoebic Abscess and Hydatid Cysts of the Liver.* **P. Czerniak, E. Lubin, M. Djaldetti, and A. De Vries (Radium and Isotopes Institute, Government Hospital, Tel-Hashomer, Israel and Department of Medicine D, Beilinson Hospital, Petah Tiqua, Israel)**

Hepatoscannings were performed in 150 patients, using colloidal Au^{198}. For better detection and localization of liver lesions a three-plane scanning technic was developed. The patients were examined in anteroposterior, lateral and postero-anterior positions. This stereohepatoscanning enabled us in 47% of cases to obtain additional findings to those detected by the usual antero-posterior technic. The results except the normal were classified into 4 groups: a) space occupying lesion; b) "foggy" liver; c) abnormal form and position of liver; d) deferred diagnosis.

Twenty-seven patients were examined twice and 6 patients 3 times, to follow the evolution of the liver disease. Special interest was devoted to amoebic liver abscess and liver echinococcus; 48 patients with these parasitic diseases were examined. In 24 of them the disease was active, the others were follow-up cases, treated 1 - 3 years ago. Among the patients with amoebic liver abscess, 7 were acute cases and 13 had suffered from this disease in the past and had been treated with emetine before they were scanned. Some of the acute cases were re-examined 2, 4, 6 months after treatment. Healing process was already evident after two months and the liver scanning was normal after 4 - 6 months. Out of the 13 cases treated 1 - 3 years ago, 10 had perfectly normal liver scannings. All the active cases of echinococcus had pathological scannographic findings. Some of these were operated and followed. Nine of 11 cases operated for echinococcus 2 - 3 years ago had abnormal findings, ranging from changes in the normal liver "silouette" to suspicion of new space occupying lesion.

The impression was gained that the healing process in the liver evolves more rapidly and completely in cases of amoebic abscess treated with emetine and chloroquine, than in cases of operated echinococcus.

20. *Criteria for Evaluating Collimators Used in In Vivo Distribution Studies With Radioisotopes.* **W. C. Dewey and W. K. Sinclair (The University of Texas M. D. Anderson Hospital and Tumor Institute, Houston)**

In many practical circumstances involving the localization of radioactive regions in the body the highest resolution is not necessarily desirable because of the accompanying reduction in sensitivity. A compromise must therefore be effected between resolution and sensitivity. Principles are presented for effecting this compromise and a figure of merit is defined in order to determine which collimator-detector system provides the highest probability of detecting a radioactive target located inside a region with a different concentration of radioactivity. A most important factor is the ratio of target-to-nontarget sensitivity, which depends on both the shielding of the detector and the collimator construction.

Three different focusing collimators having 91, 19, and 7 holes, respectively, and two single-bore collimators, 3 and 5 inches in length, are studied. It is found that the most suitable collimator for detecting a given target depends on the size of that target. For example, of the compromises available, a collimator with very good resolution and low sensitivity is best for small targets, while for larger targets a collimator with low resolution and high sensitivity is best.

Two other questions of interest are considered. First, the distortion in the representation of the target, which varies with target size, is specified in terms of a parameter called specific resolution. Second, the concentrations of radioactivity needed for given scintiscanning situations can be calculated by means of an equation which is derived. An application of the equation to a practical case in brain-tumor scanning is presented.

21. *Medical Applications of the Personal Radiation Monitor.* **R. H. Dilworth and C. J. Borkowski (Oak Ridge National Laboratory, Oak Ridge)**

The Personal Radiation Monitor is a fountain-pen-sized radiation detection device providing immediate visual and aural indication of gamma or X-ray dose rate. Weighing only 3-¼ ounces, the self-contained instrument may be worn in the pocket to warn of entry into an unexpected radiation level, or it may be used as a probe to determine the extent of shielding or collimation of a known radiation source. Indications are given by the flashing rate of a small neon lamp and the pitch of an audible tone, both of which increase in proportion to dose rate. The dynamic range of indication extends from background to 2 r/hr in the normal mode of use, and it is possible to fit the instrument with an attitude switch for range change that extends the upper limit of proportional indication to 200 r/hr merely by inverting the instrument.

Although designed originally for use in AEC establishments, the Personal Radiation Monitor has useful applications in nuclear medicine. The radiologist, using the instrument as a probe, can determine the spatial pattern of unshielded radiation or the effectiveness of shielding. In isotope therapy the device is useful for quickly identifying the location and relative danger of radioactive preparations or excreta. It is particularly useful in determining the extent of accidental spills of such fluids. In teletherapy the routine use of the instrument could prevent accidental entry by attendants into an area of high dose rate, and it would have value in determining the spatial location of highly collimated gamma beams.

The instrument operates continuously for one month in background from a four volt mercury battery. A three transistor circuit generates 500 volts for operation of a miniature geiger counter detector. A hearing aid earphone with a resonant air column provides the source of audible alarm tone.

22. *A Study of the Effect of I^{131} Radiation on Cell Division in the Thyroid Using Tritiated Thymidine.* **Brown M. Dobyns and Mary Ann Jenkins (Western Reserve University College of Medicine, Cleveland)**

The effect of I^{131} radiation has been under study in this laboratory for some time. Short of serious destruction of thyroid tissue, there is interference to cell division which results in either a failure of mitosis or mitosis resulting in bizarre nuclear forms. These changes were studied in another way using tritiated thymidine, which is incorporated into DNA preliminary to cell division. Radioautography was used to demonstrate those cells in the process of division.

After an introductory period of iodine deficiency to produce good uptake and hyperplasia, rats were given doses of 0, 5 or 50 μc of I^{131}. Tritiated thymidine was injected four hours before the animals were sacrificed. Control animals with hyperplastic thyroids from iodine deficiency showed abundant nuclei bearing the tritium label, indicating active DNA synthesis. Within 20 hours after 5 μc of I^{131} thyroids showed reduced numbers of labelled nuclei, indicating significant retardation of cell division. Nuclei containing tritium were very rare in the 50 μc animals at this time.

Serial observations in the 5 μc animals days and weeks after I^{131} (using thiouracil as a stimulant), showed a tendency to recover from the impairment to mitosis after two months. After the same interval, the animals that received 50 μc failed to take up the tritium label and failed to hypertrophy after the administration of thiouracil.

Observations over longer periods of recovery are also presented.

23. *Some Applications of Radioactive Isotopes in Renal Function.* **Rafael Dominguez (Department of Pathology Research, St. Luke's Hospital, Cleveland)**

The continuous monitoring of the blood concentration and of the urine excretion of a substance primarily excreted by the kidney affords the opportunity to answer a number of questions both on kinetics of compartmentalized systems and on renal physiology. The experimental arrangement consists in the preparation of an arteriovenous shunt with the shunt coiled around a scintillation crystal. By means of a counting rate meter and of a digital printer the activity of the blood in counts per minute, and the integral of this rate between pre-assigned time limits are both obtained. The ureters are catheterized and securely tied and the urine is collected (either separately or jointly). The arterial blood pressure and the pressure in the venous end of the shunt are both measured and recorded. The isotopes, I^{131} Diodrast and I^{131} Urokon, can be administered in a variety of ways, but this presentation is limited to (1) a single rapid intravenous dose and (2) a continuous infusion at a constant rate. Some of the applications of this technique are reviewed.

1) In the simple two campartment system in which we measure the concentration of the isotope in compartment I and the amount excreted by the kidney, the concentration in compartment II is calculated. The calculation indicates that in the neighborhood of the maximum concentration in the second compartment, and thereafter, the concentration in the second compartment is higher than the concentration in the first compartment. The existence of this gradient can be demonstrated by clamping both renal arteries sometime after the calculated maximum in the second compartment is attained.

2) After an interval of one or two hours during a constant rate infusion of radioactive material into the blood an equilibrium position is reached between the rate at which the material is being injected and the rate at which the material is being eliminated. Since with Diodrast 90% or more of the material is eliminated by way of the kidney, the maintenance of a plateau is for practical purposes an indication of the maintenance of renal excretory activity. The animal preparation is, from this point on, a sensitive indicator of changes in renal function. By means of this technique we show:

a) the effect of Benemid on both I^{131} Diodrast and I^{131} Urokon

b) the tolerance of the kidney to a total arterial ischemia of ten minutes duration

c) the lack of tolerance of the kidney to a complete occlusion of the renal vein for ten minutes

d) the large reservoir of the renal tubules in ureteral obstruction

e) the establishment of pyelovenous communications during ureteral obstruction.

24. *The Radiorenocystogram in Upper Urinary Tract Infections.* E. K. Dore, D. E. Johnson, and G. V. Taplin (Laboratory of Nuclear Medicine and Radiation Biology of the Department of Biophysics and Nuclear Medicine, and the Departments of Radiology and Medicine, School of Medicine, University of California, and the Los Angeles County Harbor General Hospital, Torrance, California)

Standard medical and radiographical procedures seldom detect important functional disturbances which may be associated with infections of the upper urinary tract, namely ureteral spasm, partial urinary obstruction and minor impairment of tubular cell function. The renocystogram performed with I^{131} labeled Hippuran is capable of detecting these abnormalities directly. Moreover, serial tests made during the course of therapy with specific antibiotics have demonstrated that all of these functional disturbances may be completely reversible.

Serial renocystograms were performed in a large group of patients having renal diseases in all degrees of severity, including acute anuria. Standard tests of total renal function including blood urea nitrogen, urea clearance, the 15-minute PSP excretion test and intravenous pyelograms were performed simultaneously and repeatedly along with the renocystogram and the 15-minute Hippuran I^{131} excretion tests. The relative merits of the tracer procedures were evaluated by comparison with accepted biochemical and radiographical methods. The interpretations of these findings will be presented along with selected case reports which illustrate the usefulness of serial renocystograms in the management of patients with upper urinary tract infections.

25. *Medical Qualifications for Nuclear Medicine.* Lee Farr (Medical Division, Brookhaven National Laboratory, Upton, Long Island, New York)

26. *The Binding of I^{131} Labeled Contrast Media by Human Serum.* Richard S. Farr, Elliott C. Lasser, and Gerald P. Rodnan (Departments of Medicine and Radiology, University of Pittsburgh, Pittsburgh)

The binding between human sera and three I^{131} labeled contrast media was studied by means of equilibrium dialysis. Aliquots of 1:5 dilutions of human sera were dialyzed at room temperature against 10^{-4} to 10^{-6} molar solutions of contrast media. In addition to the contrast media, the outside bath also contained 0.8% dextran in isotonic saline-borate buffer at pH 7.4. Under these conditions, it was found that human sera bind considerable amounts of Iodipamic acid (Cholografin) and sodium acetrizoate (Urokon) but almost no affinity was demonstrated between human serum and sodium diatrizoate (Hypaque). Cholografin and Urokon probably compete for the same receptor site on human albumin, but Cholografin forms a much stronger bond with albumin than does Urokon. The interaction between Urokon and albumin was highly specific in the sense that the only difference between Urokon and Hypaque is the addition of an acetylamino group at the fifth position on the benzene ring. Another evidence of specificity can be shown by the fact that, in contrast to human serum, rabbit serum binds very little Urokon. These observations along with other data to be cited support previous suggestions that contrast media with strong albumin bonds are excreted preferentially into the biliary system whereas contrast materials with little or no albumin binding are most easily excreted by the kidney.

27. *Scanning With a Compact Transistorized Scintillation Detector and Polaroid Recording.* **Theodore Fields, G. Clayton, J. Kenski, and Ervin Kaplan (Radioisotope Service, Veterans Administration Hospital, Hines, Illinois)**

Earlier reports published by this laboratory demonstrated the feasibility of employing a simple transistorized light amplifier for radiation scanning. Briefly, the unit consists of a scintillation crystal, photomultiplier, high voltage pack, and a transistorized amplifier pulsing a subminiature indicator triode. The readout was accomplished by means of recording on Polaroid film.

Subsequent investigations have centered about improvement in the readout, scanning mechanism, collimation, and electronics. Results of early tests with electroluminescent mosaic plates are promising. Mosaics of 16 lines per inch (256 bits per square inch) are being tested with good visual accuity.

Rapid repeating spiral scanning patterns are being investigated for an economical, compact and prompt mechanical system. Focusing collimations employing a few crystals in the holes are being tested and the results will be reported. In addition, the transistorized amplifier now employs an integrator circuit which allows for the best selection of information bit factors.

The many problems being investigated are all directed toward making the scanning device a more practical and economical tool in the nuclear medical practitioners regime.

28. *Radiological Safety and Protection.* **Theodore Fields (Radioisotope Service, Veterans Administration Hospital, Hines, Illinois)**

The control of radiation exposure is discussed as affected by current recommendations of accepted regulatory agencies. Pertinent releases of AEC, USPHS, NBS and other cognizant authorities are reviewed.

Routine accepted clinical radioisotope techniques are discussed from the safety viewpoint of the patient, physician, laboratory and hospital personnel, and non-radioisotope personnel. Precautions and protection for the various persons involved with these procedures are explained.

In addition, problems of instrumentation, records, waste disposal, incineration, and transportation of radioisotopes are presented and possible solutions offered. Emphasis is placed on the routine clinical radioisotope laboratory problems and their most economical, feasible, and quick solutions.

29. *The Effect of Total Body Gamma Radiation on the Fibrinolytic System of Lung—Relationship to Hyaline Membrane Formation.* **William H. Fleming, LT, MC, USN, Jeno E. Szakacs, LCDR, MC, USN, and E. Richard King, Captain, MC, USN (Department of Nuclear Medicine, U. S. Naval Hospital, Bethesda)**

The fibrinolytic system is considered important in the normal physiology of lung. It is through this system that the body converts by means of activators, inactive circulating plasminogen to plasmin, the active fibrinolytic enzyme. Normal lung contains large amounts of plasminogen activator. This activator is relatively insoluble and hence its action is primarily local. In situations where fibrin may be deposited in an alveolus, it is the function of lung plasminogen activator to convert plasminogen to plasmin and effect fibrinolysis. In lung, defects in this system are associated with hyaline membrane formation.

Observations on human lung from three patients receiving Total-body Radiation (TBR) revealed hyaline membrane formation and absent lung plasminogen activator. These patients received 450 r, 600 r, and 1500 r TBR. Data from over twenty dogs exposed to gamma radia-

tion are consistent with the production of a potent inhibitor to plasminogen activator. These dogs have been subjected to 600 to 1000 r TBR and 1500 to 2000 r hemithorax radiation. The influence of Cortisone, Actinomycin D and Heparin will be presented.

30. *Value of Tagged Hemoglobin in Reticulo-Endothelial Studies.* ELEMER R. GABRIELI, ALONZA JOHNSON, MANUEL SCHREIBER, PHILENA HECKERT, and ALICE ELLIOTT (The Millard Fillmore Research Institute, Buffalo)

Hemoglobin, biolabeled with Fe^{59} or in vitro tagged with I^{131} was employed to explore its catabolisms after being intravenously injected in the rat. Selective removal of hemoglobin by the hemovascular part of the reticulo-endothelial system was readily demonstrable with the tagged hemoglobin. Decrease in radioactivity of the blood is a rapid and complex phenomenon. Fe^{59} and I^{131} labeled hemoglobin leave the circulation at the same rate initially, but soon progressive difference becomes apparent, with consistently higher I^{131} levels. This difference is exaggerated when nephrectomized rats are used; as early as 15 minutes after administration of labeled hemoglobin considerable amounts of free I^{131} are found in the blood.

The kinetics of intracellular catabolism of the phagocytized hemoglobin is reflected by rapid splitting of the radioactive tag. The rate of clearance of I^{131} labeled hemoglobin, together with liberation of the I^{131}, seem to offer an interesting approach to reticulo-endothelial functions. Striking species differences are found when these data are compared with those obtained in similar studies on humans.

31. *Renal Blood Flow Measurement From Blood Clearance of a Single Injection of Hipputope.* FRANK STOREY GOTT, WALTER H. PRITCHARD, WILLIAM R. YOUNG, and WILLIAM J. MACINTYRE (Department of Medicine, Western Reserve School of Medicine and University Hospitals, Cleveland)

These studies have shown blood concentration—versus—time curves after a single injection of Hipputope (radioactive ortho-iodohippuric acid, Squibb) consistently follow a 3-phase pattern (40 patients). In the curves, plotted from serial blood samples, the 0 - 3 minute section of the curve is steep as Hipputope is mixing and leaving the blood through renal clearance, rapid diffusion into an extracellular space (#1), and take-up by a final equilibrium space (#2). The 3 - 9 minute phase is a quasi-exponential sum of exponential renal clearance and continue take-up into the additional space #2. The 9 - 25 minute phase represents the exponential renal clearance of the tracer from all compartments as the diffusion into and out from the extravascular spaces appears to be very rapid. The total apparent volume of dilution is thus calculated by extrapolation of the third slope back to zero time. The product of this volume and this slope (observed 10 to 20 minutes after injection) is the effective renal blood flow.

Correlation with results simultaneously obtained with the classical PAH clearance method has given a 95% confidence interval for the difference of −10.0% to +9.4%. The average difference was 5.5 (2.4 - 8.7)%.

Simultaneous recording of concentration over both kidneys can be correlated to the total renal blood flow in order to estimate individual renal blood flow. The comparison of the observed clearance slope of the blood to the slopes observed at each kidney yields information regarding its excretory action. No urine collection is needed and the test can be performed quickly.

32. *Therapy of Malignant Serous Effusions With Radiottrium (Y^{90}).* JOSEPH GREENBERG and H. C. DUDLEY (Department of Nuclear Medicine, New York Polyclinic Medical School and Hospital, New York)

Radioactive yttrium (Y^{90}) is a radiometal with ideal characteristics for intracavitary application. It is a 2.18 Mev pure beta emitter with a half life of 61 hours, forms insoluble complexes with nucleic acids and has a strong affinity for chelating agents. When properly

prepared (there must be at least 200 mg Y^{89} as carrier) there is essentially complete localization in the treated cavity and 30-40 mc will frequently result in the elimination of the effusion. There are no significant side effects or intracavitary fibrosis post therapy. The material is easy to handle and the after care of the patient uncomplicated. The therapeutic results compare very favorably with other modalities being used. The technique of preparation of the material is presented.

33. *Clinical Experience with I^{125}.* Paul V. Harper, Harold Endlich, Katherine A. Lathrop, and Warren Siemens (Argonne Cancer Research Hospital, University of Chicago, Chicago)

The many suggested advantages of I^{125} have led us to explore its use in clinical studies. The isotope available from the cyclotron activation of tellurium is heavily contaminated with I^{126} and unsuitable for human use. I^{125} produced in our laboratory in 200 to 300 mc quantities by neutron activation of Xe^{124} is free from this objection and is being used routinely in patients at The University of Chicago Clinics. Although I^{131} and I^{125} produce approximately the same dose in rads per microcurie destroyed per gram of tissue, the 60 day half life of I^{125} allows removal of most of the material from the body before decay, thus greatly reducing the radiation dose to the patient, which can be significant especially in thyroid scanning. It was found that with unmodified equipment, thyroid scans of equal quality and liver scans of superior quality could be obtained with the same microcurie dose as with I^{131}. With special probe design an additional factor of five or more in sensitivity should be attainable. Thyroid uptake studies presented difficulties due to variable self absorption in the neck. Studies involving the counting of small *in vitro* samples present no problems. I^{125} may be assayed accurately by the coincidence method using an ordinary well counter. The K_x-K_x and K_x-γ coincidences are easily seen by the crystal scanning method using integral bias counting. It appears that higher tolerable isotope dosage, higher scanning resolution and lower radiation dosage are among the advantages which accrue from the substitution of I^{125} for I^{131}.

34. *An Automatic Electronic Method of Analyzing Scan Records.* C. C. Harris, P. R. Bell, and J. E. Francis, Jr. (Oak Ridge National Laboratory, Oak Ridge)

A novel use of a transistorized aural counting rate indicator shows promise in the process of analyzing scan records. Information in dot-patterns and digital photoscans is usually unprejudiced. However, the area over which the eye integrates information tends to be fixed. This device allows choice of an optimum integration area, and provides a method of analysis which does not alter the original data.

A light-sensing device (a silicon solar cell) is coupled to an aural counting rate indicator (howler) so that the frequency of a tone can be varied over a wide range in response to variations in light striking the light-sensor.

A pulse output is available to drive printers. This device, with a selection of apertures which define the area seen by the sensor, has been used to examine certain scan records. The records are placed on a light box, and the sensor used to "read" variations in density. The rescanning has been done by hand, and automatically by attaching the light sensor to a scanner, and printing new records with the pulse output.

It is found that the "ear can hear" information that is missed by the eye. The "re-scan" records show significantly more information than originals and are easier to interpret. The frequency range of the howler is from zero to 15,000 cycles, and since zero frequency can be set at any chosen light level, the device is extremely sensitive to small changes in light transmitted through the record.

35. *Internal Dose in Humans.* **R. L. Hayes and W. R. Butler, Jr. (Medical Division, Oak Ridge Institute of Nuclear Studies, Oak Ridge)**

Previous beta dose studies with live dogs where glass dosimeters were implanted in the walls of the intestinal tract showed the expected variations between individuals when the dogs were in a normal state; however, when the intestinal motility was experimentally altered, the average doses for the extremes from normal behavior varied by a factor of 20. For selected individuals the factor was as great as 45. This result has raised the question of the validity of assuming average behavior in calculating MPC values (NBS Handbook 69) where the human intestinal tract is the critical organ. Direct dose measurements in man are impractical; however, by employing a tracer technique it is possible to estimate the maximum beta dose that could have been received by any one individual. Using this approach an estimate of the range of variability from "MPC average behavior" for a large group of individuals could be obtained and in turn the validity of assuming an "average behavior" could be assessed. The preliminary results of this type of study using lanthanum-140 (an isotope only slightly absorbed from the intestinal tract) show in the majority of the individuals tested a good agreement with predicted dose; however, the spread from lowest dose to highest dose has been a factor of 10.

36. *Renal Scintigrams in the Diagnosis of Renal Vascular Disease.* **Thomas P. Haynie, Mohamed M. Nofal, Edward A. Carr, Jr., and William H. Beierwaltes (Departments of Internal Medicine and Pharmacology, University of Michigan Medical Center, Ann Arbor)**

Interest has heightened, recently, in vascular renal lesions as a cause of hypertension. Scintillation scanning of the kidneys offers a method for visualizing such lesions. In this study the diagnostic efficiency of photoscans and dot scans has been compared with that of pyelograms and aortograms. Experimental lesions in dogs at sacrifice and pathologic findings in humans at operation have been correlated with the renal scintigram. We have used I^{131} labeled iodohippurate (Hippuran) or Hg^{203} labeled chlormerodrin (Neohydrin) with a dot scanner and a photoscanner to make scintigrams of dog and human kidneys having vascular lesions. Using radio-iodohippurate, the scan was begun 20-30 minutes after starting an infusion of 200 μc at a rate of 2-4 μc/minute. Using Hg^{203} chlormerodrin, scans were started 40 minutes after a single intravenous injection of 100 μc. To date, scans performed on 5 dogs before and at intervals after the experimental production of renal infarcts suggest the diagnostic usefulness of this technique. Satisfactory scans have also been obtained on 7 patients, using radio-iodohippurate in 4 patients and Hg^{203} chlormerodrin in 3 patients. Four of these patients subsequently had renal surgery, and in 3 instances the renoscan findings coincided with the findings at operation while aortography correctly predicted the operative findings in two patients and pyelography regularly failed.

37. *An Improved Display Method for Scintiscanning.* **Fred C. Heagy, Arthur Vaart, and John C. F. MacDonald (The Ontario Cancer Foundation London Clinic, Victoria Hospital, London, Ontario, Canada)**

In an attempt to eliminate some of the disadvantages of conventional scintiscanning systems, the output of the pulse height analyzer is used to trigger the electron beam in a five inch cathode ray tube. The horizontal and vertical positions of the electron beam are controlled by the position of the scintillation detector. The illumination of the cathode ray tube is recorded on a 4″ x 5″ film. The advantages of this system are: 1. All the information from the analyzer is recorded as it is produced. 2. The time lag involved in a system that uses a ratemeter in the electronic control circuit is avoided. 3. The time lag involved in a system that uses a tungsten filament lamp for photorecording is avoided. 4. Because of the instantane-

ous response it is possible to scan more rapidly and to scan in both directions. 5. The controls for spot size and illumination are very flexible. 6. The information is recorded on a film small enough to fit into a commercial television analyzer which is used for contrast variation.

38. *Concomitant Radioisotopic and Radiography Cerebral Arteriography.* JAMES JACKSON, BARNES WOODHALL, GEORGE J. BAYLIN, RONALD KRUEGER, and AARON P. SANDERS (Departments of Surgery and Radiology, Duke University Medical Center, Durham, North Carolina)

A group of neurological patients in which tumors, hemorrhage or strokes were suspected comprised the study group. The common carotid artery of the neck was punctured percutaneously using local anesthesia. The usual placement of the needle was antergrade. In some instances it was placed retrograde on the right side to obtain veretebral filling.

In all instances the contrast media used was 50% hypaque (8 ml per injection). Conventional lateral and AP stereo roentgenograms were obtained. Between the lateral and AP arteriograms a radioisotopic study of the circulation pattern was made.

Twenty microcuries of I^{131}-labeled hippuran in a 0.25 ml volume was manually injected into one orifice of a three way stopcock and immediately followed by an 8 cc injection of isotonic saline through the third orifice.

The collimated scintillation detectors were directed into the vertex of the skull. Each detector was collimated in such a manner as to "see" only one half of the cranium. The output of each detector was fed to a count rate meter and then to a rectilinear strip chart recorder.

The comparison of the arteriograms with the radioisotopic circulation studies will be discussed.

39. *A Descriptive Analysis of Vascular Beds.* JOSEPH M. JAMES, ALLEN M. LESAGE, G. S. EADIE, and W. GLENN YOUNG (Department of Radiology, Surgery, and Physiology, Duke University Medical Center, Durham, North Carolina)

Surgical techniques for extra corporeal circulation are used to delay recirculation of a radioactive plasma label I^{131} by temporarily diverting the return flow from an organ or other region into a second reservoir and maintaining the circulation from a reservoir containing unlabeled blood. Detection is accomplished by passing the return flow through a glass coil surrounding sodium iodide crystal, fed to a count rate meter then to an Easterline Angus strip recorder. The record, 2 to 3 minutes long, can be regarded as a frequency diagram of pathway times between the point of injection and that of observation.

As an example of studies made possible by this technique curves are shown of the systemic flow in dogs at normal body temperature and at 10° C. At normal temperatures the curve consists of an initial peak of fairly constant form followed by a variable plateau. At low temperatures the initial peak is delayed and is followed by a smooth fall resembling an exponential curve. The significance of these changes in shape is discussed.

40. *Radioautography, Principles and Procedures.* DAVID L. JOFFES (Cancer Research Institute, New England Deaconess Hospital, Boston)

To the radiobiologist the term "radioautography" denotes a method of studying the distribution of radioisotopes which have become incorporated in an organism by observing the patterns created when the radiation from the isotope impinges upon a photographic film placed on or near the tissues. Depending on the isotope used accurate determinations of the sites of deposition and concentration of isotopes in organs, tissues and cells can be made by means of radioautography. Several variations of the techniques of radioautography have evolved: placing a photographic film (with its backing) in apposition with an histologic slide, floating the film (free of its backing) onto the tissue, mounting the tissue directly on a cut

film instead of a slide, painting the melted film emulsion over the tissue on a slide, as well as others, and combinations of these techniques. The most generally applicable method is the dipping technique which offers speed and ease of preparation unsurpassed by any other radioautographic technique and gives as good point to point localization and resolution as the best. Ordinary histological slides are used, avoiding preparation in reagents in which the isotope bearing compounds in the tissue are soluble. Staining is best performed after photographic development. Appropriate nuclear film emulsion obtained in bulk is melted in a water bath at 40° C. The slides are rapidly individually dipped into the emulsion; the bottoms cleaned of emulsion; and slides placed horizontally on trays in an exposure box at room temperature, in an atmosphere of CO_2 or N_2 at 15% relative humidity or less to reduce latent image fading. Exposure time is determined by developing samples of replicate slides at intervals until the optimum is apparent. Development is carried out at 18° C ± 1° in fresh Kodak D 19 developer, 1 minute; SB5a stop bath, 15 seconds; acid hardening fixer, twice clearing time; and tap water wash, 30-60 minutes. A series 1 safelight may be used. After washing the slides are stained, cleared and coverslips mounted.

41. *Evaluation of Tracer Methods for Estimating Coronary Blood Flow.* D. E. Johnson, C. K. Liu, G. V. Taplin, and E. K. Dore (Laboratory of Nuclear Medicine and Radiation Biology of the Department of Biophysics and Nuclear Medicine, and the Department of Radiology and Medicine, School of Medicine, University of California, and the Los Angeles County Harbor General Hospital, Torrance, California)

Two new tracer methods for estimating the efficiency of the myocardial blood supply have been introduced recently by Sevelius and Johnson, and by Mena, Bennett and their associates. Both methods are performed externally with scintillation detection and recording equipment to register the first passage of a tracer material through the heart and a selected area of the peripheral arterial circulation. Sevelius and Johnson used two ratemeter-recorder systems with one detector placed over the heart, the other over one kidney. Information from the latter is used as an aid to identify the coronary component of the heart curve. The coronary blood flow is estimated by comparing the areas under the heart curve and its coronary segment. Mena and Bennett used two events per units time (EPUT) systems to register changing levels of radioactivity from detectors placed over the heart and the occipital region of the head. The exponential curves of best fit and the half-time values for each were determined. The ratio of heart-to-head half-time values is considered to be an *index* of coronary blood flow.

Numerous technical and instrumentation problems were encountered in attempting to apply these methods directly. However, because of their great diagnostic and research potential, further investigation was considered worthwhile. Phantom studies have demonstrated the validity of the physical basis of these tests. Animal experiments were performed to determine the detectability of surgically produced abnormalities of coronary blood flow. Comparative clinical trials were made in large numbers of normal subjects and patients with proved coronary insufficiency, using the two original methods and new modifications. The present status of these methods will be discussed regarding their validity, accuracy, reproducibility and clinical usefulness.

42. *Myocardial Blood Flow of Patients Submitted to Vascular Surgery.* Philip C. Johnson, Jr. (Radioisotope Laboratory, The Methodist Hospital, Houston)

Myocardial blood flow by the diodrast I^{131} surface counting method has been used to evaluate 50 patients who had major cardio-vascular surgery. Approximately 50% of these patients had symptomatic arteriosclerotic heart disease which was better correlated with decreased myocardial blood flow values than with changes in the electrocardiogram. A lack of correlation was found between the degree and symptoms of peripheral atherosclerotic involve-

ment and coronary atherosclerotic involvement as shown by decreases in myocardial flow. Aortic aneurysms were found to slow the left heart to peripheral circulation time from a normal of less than 0.5 seconds to over 4 seconds. Slowing was not found above the aneurysm and disappeared after surgical removal of the aneurysm demonstrating that even patent aneurysms markedly interfere with aortic blood velocity peripheral to the aneurysm.

Mean myocardial blood flow of those patients without cardiac symptoms was 5.1 ± 0.4% of cardiac output. Those patients with cardiac symptoms had a mean myocardial blood flow of 3.0 ± 0.3%. This compares with a group of young normal men: 6.1 ± 0.3% and patients under treatment for angina pectoris: 2.3 ± 0.2%. All means are statistically different $P < .05$.

Myocardial blood flow estimated during surgery and immediately after showed that both cardiac output and coronary blood flow are maintained generally at levels equal to control.

In conclusion estimation of myocardial blood flow can be used in the evaluation and follow-up of patients submitted to major vascular surgery and it gives information of clinical value not obtained by other means.

43. *On Being Well Named—Discussion of Standard Nomenclature for Radioisotope Procedures.* Ervin Kaplan (Radioisotope Service, Veterans Administration Hospital, Hines, Illinois)

The need for a standardized nomenclature for diagnostic, therapeutic and investigative procedures using radioisotopes is recognized. The proper identification of procedures on hospital charts, AEC applications, publications and public presentations, would be of great aid in preventing confusion and misunderstanding.

The need for physiologic criteria in terminology is accepted, but represents only a fragment of the problem involved. The appropriate classification scheme should be a generic one, recognizing the isotope, physical or chemical form, the organism or portion of the organism involved, the function being studied as well as the specific means employed in making the evaluation. In addition, the author of the test may be recognized by a parenthetical terminal inclusion—a most appropriate place for an author. In schematizing isotope therapy, the disease being treated and the route of administration should also be included.

The organization of the classification must be simple enough to allow for numerical coding to adopt properly to informational classifying and correlative systems. The classification must be sufficiently generalized to permit the naming of any new procedure.

A Central Nomenclature Registry might be organized—perhaps a function of the Research and Education Committee of the Society of Nuclear Medicine. This Registry would receive, name, record and publish the nomenclature of the various procedures, perhaps as a periodic publication in, or supplement to, the *Journal of Nuclear Medicine.*

44. *Evaluation of Two Compartment Systems by Continuous Gamma Monitoring of a Dialysis-Perfusion Device.* Ervin Kaplan and John J. Imarisio (Radioisotope Service, Veterans Administration Hospital, Hines, Illinois)

Employing a scintillation NaI(Tl) well detector, count rate meter and recorder assembly. it is possible to monitor the escape rate of a diffusible radioactive substance from a dialysis bag. In the method being described, a one ml "Visking" bag is one compartment contained within a second compartment, a test tube, in the well counter. A reservoir of dialysate continually replaces the fluid in the second compartment at a rate effectively preventing back diffusion into the "Visking" bag.

The rate of diffusion for a single molecule or ion is logarithmic in nature and is influenced by temperature, particle size, transference, membrane porosity, pH, concentration and charge effect. The presence of a large molecule, crystal, cell or aggregate not capable of penetrating the membrane will alter the escape rate of a permeable labeled substance which may be bound to the non permeable material. The difference in rate loss is proportional to a dissociation constant. If binding capacity is exceeded, the initial rate of loss is enhanced and may quantitate

binding capacity. The effect of non radioactive substances which alter binding or dissociation, may be studied in this system, and may be exemplified by lytic enzymes.

The system may be reversed and the "Visking" bag used as a sterile perfusion chamber, allowing study of trapping of gamma emitting isotopes, by protein molecules, cells or tissue fragments.

Current investigation of thyroid hormone binding is underway with this device. The generalized method presented appears applicable for the study of many living and non living systems. It would be further improved by modification, allowing detection of beta emitting isotopes.

45. *Determination of the Specificity of Antibody Response to Endotoxin by Precipitation of Cr^{51}-Labeled Endotoxin.* D. Koch-Weser (Department of Medicine, Western Reserve University School of Medicine, Cleveland)

Even though antibody formation after repeated injections of endotoxins (bacterial lipo-polysaccharides) has been described, its role in the production of "tolerance" has been considered secondary to reticulo-endothelial activation.

By labeling lipo-polysaccharides from E. coli, salmonella typhosa, staphylococcus aureus and streptococcus group A with Cr^{51}, it has been demonstrated that these endotoxins are precipitated *in vitro* by antibodies in the serum of rabbits made "tolerant" by repeated injections of bacterial lipo-polysaccharides. The antibodies were shown to be gamma-globulins and combining in the precipitate with the antigens (endotoxins) rendered these inactive, as measured by inability of the complex to produce a Schwartzman reaction.

The specificity or non-specificity of the antibody-formation against these different antigens was easily determined. As examples Cr^{51} labeled lipo-polysaccharide from E. coli precipitated in the serum of rabbits made tolerant with injections of E. coli endotoxin, but did not react with antibodies in the serum of rabbits immunized with either paracolon or salmonella typhosa endotoxin.

Cr^{51} labeled lipo-polysaccharide from S. typhosa, however, precipitated also in the serum of rabbits treated with paracolon.

The method is promising for determining the role of immunity on gram-negative infections, and for investigating means to produce specific and non-specific tolerance.

46. *Thyroid Function and Hepatic Injury by Cerium.* Granvil C. Kyker, John Rafter, and Fred Snyder (Medical Division, Oak Ridge Institute of Nuclear Studies, Oak Ridge)

We have described an acute but transient hepatic injury caused by cerium and other lanthanons. Specific metabolic knowledge is meager for these and other nuclear minerals which offer both potential medical application and hazard. Fatty infiltration prominently reflects the metabolic upset that we have observed and a broad scope of factors modify or prevent it. Among these, endocrine disturbances are especially noticeable including orchectomy, hypophysectomy, adrenalectomy, and alloxan diabetes. We are now reporting the effect of thyroid function on liver lipids after intravenous cerium (2 mg Ce per kg, as chloride) in rats (young adult, CFN, female). Normal and thyroidectomized rats, prepared surgically and by radioiodine, were compared. Basal metabolic rate and external scanning served to evaluate the prepared animals. Loss of thyroid function prevented the increase in liver lipids caused by cerium. Related considerations of energy metabolism prompted measurements that suggest a large intake of carbohydrate also to be protective. This additional scope to factors that modify or prevent rare-earth fatty liver extends the metabolic involvement of nuclear minerals.

47. *Pituitary Alpha Particle Irradiation.* JOHN H. LAWRENCE, CORNELIUS A. TOBIAS, and JAMES L. BORN (Donner Laboratory and Lawrence Radiation Laboratory, University of California, Berkeley)

Ten years experience in the use of 900 million volt alpha particles from the 184-inch cyclotron for the inhibition of, the function of, or the destruction of, the pituitary gland in various clinical states will be discussed. These will include metastatic mammary carcinoma in women and men, metastatic prostatic carcinoma, malignant diabetes with advanced retinopathy, malignant exophthalmus, and tumors of the hypophysis. Discussion includes the characteristics of the irradiation, the experimental setup, details of clinical, metabolic, and investigative studies on these patients including isotopic techniques used before and at various periods following irradiation.

48. *"Blind End" Technique for Iridium-192 Removable Nylon Ribbon Interstitial Implants.* LEONARD M. LIEGNER (St. Luke's Hospital, New York)

A new technique is presented which permits the interstitial implantation of radioactive Iridium sources into deep seated pelvic tumors without the need of operative exposure of the diseased areas.

Recurrent pelvic disease when deemed unresectable or unexplorable is now amenable only to external irradiation or intravaginal cone therapy. In some limited circumstances Radium implantation of accessible disease in the perineal vaginal site is feasible. The "Blind End" technique enables deep pelvic disease to be adequately implanted.

The technique utilizes guide needles preparatory to the actual implantation of radioactive seeds thereby enabling the radiation therapist to accurately implant the cancer area. Furthermore, personnel receive exposure to ionizing radiation through only that stage of the procedure when the radioactive ribbons are threaded into the guide needles.

Case histories with accompanying slides demonstrating the technique are presented. Indication and contraindication are discussed.

49. *The Clearance of Labeled Compounds as a Measurement of Hepatic Flow Versus Function.* WILLIAM J. MACINTYRE, DIETER KOCH-WESSER, JAMES H. CHRISTIE, and GODOFREDO GOMEZ CRESPO (Radioisotope Laboratory, Highland View Hospital, Cleveland)

In vivo measurements of the disappearance of colloidal gold^{198} and Rose Bengal (I^{131}) from large vascular pools have corresponded closely to a two-phase exponential clearance. Solution of this equation for the fractional clearance constant of the most rapid phase has made possible the use of colloidal gold for calculation of hepatic blood flow, irrespective of the distribution of colloidal particle size, as long as sufficient particles cleared with 100% efficiency are present.

Ratios of the primary clearance time for colloidal gold as compared to the primary clearance factor of Rose Bengal have been calculated in order to give the removal efficiency of Rose Bengal. Efficiencies have been measured in some fifty patients, including normal, cirrhotic, fatty livers and various phases of advanced liver diseases. In each case simultaneous hepatic blood flows have been obtained in order to normalize the efficiency in terms of functional blood flow to the organ.

On this basis, determination of colloidal gold clearance and Rose Bengal removal on the same patient, differentiation may be made of decreased blood flow with normal hepatic function, normal blood flow with decreased hepatic function, and impairment of both.

50. *The Influence of Protein Patterns on the Erythrocyte Uptake of I^{131}-Triiodothyronine.* **GEORGE B. MCADAMS (Hartford Hospital, Hartford)**

The *in vitro* incorporation of I^{131}-Triiodothyronine into erythrocytes has proven valuable as a test of thyroid function. Since this uptake by red blood cells is an indirect measurement of the relative saturation of thyroxine-binding protein, (inter-alpha globulin) and to a less extent of albumin, alterations in the amounts of these circulating proteins influence the results of this test. In this paper an explanation of the principle underlying the T3 test is given, together with mention of the inherent difficulty presented by variations in concentrations of protein fractions. A review of approximately 1800 T3 determinations at the Hartford Hospital for the two years, 1958-1960, is presented with a discussion of reasons for those results which were elevated in euthyroidism. Electrophoretic patterns are demonstrated and the value of obtaining serum protein patterns in cases of unexplained high T3 values is discussed.

The effect of the change in serum protein patterns in pregnancy has been utilized in the T3 test as a laboratory aid in the diagnosis of early pregnancy. The T3 values in 42 cases of normal and abnormal pregnancies at the Hartford Hospital are reviewed with special reference to values before and after hormonal therapy in threatened abortions and in hydatidiform moles. Corresponding electrophoretic patterns in 7 cases are presented. It is concluded that the T3 test can be a valuable laboratory adjunct in predicting threatened abortions in cases of bleeding from hormonal disturbances during the first trimester.

51. *The Future of Nuclear Medicine.* **JOHN MCAFEE. (Johns Hopkins University Hospital, Baltimore)**

Despite considerable interest during the past decade, radioisotopes used both diagnostically and therapeutically have failed to create a sizeable impact upon the practice of medicine. Many large institutions continue to regard radioisotope laboratories as a research luxury rather than a necessity for good patient care. Within the next decade this attitude will probably change drastically as the gap narrows between nuclear physics and instrumentation, and their medical applications. The use of radioisotopes in clinical research will parallel the impact of radioactive tracers upon basic biochemistry. The role of radioactive tracers in clinical medicine of the future will probably become equal in importance to that of X-ray diagnosis and therapy.

For nuclear medicine to live up to these expectations, many difficulties in present day practice must be overcome. Laboratories must develop additional facilities designed solely for training of personnel. Full-time professional staffs must devote more time to adequate training of physicians. Radionuclides and labeled compounds available for the physician's use, currently quite limited in number, must be increased in number. The present day instrumental facilities of most laboratories include only a few types of gamma detectors. Other instruments will be required to permit use of a wide variety of compounds labeled with beta emitters in diagnostic studies. The rapid advances in instrumental design may reach a plateau in the years ahead, but the era of radiochemistry as applied to medical problems has just begun.

52. *Hematologic Events as Dosimeters in Total-Body Radiation.* **WILLIAM MCFARLAND, CDR, MC, USN, and HOWARD A. PEARSON, LCDR, MC, USN (Department of Nuclear Medicine, U. S. Naval Hospital, Bethesda)**

The difficulties encountered in judging the amount and type of radiation involved in an accidental exposure are well recognized. Such difficulties might be resolved by the development of better monitoring systems or by controlled studies relating specific clinical developments to specific amounts of ionizing radiation.

In the present study we have had the opportunity of observing hematologic events in a group of patients receiving total-body gamma radiation from a multiple Co^{60} source in doses

from 225 to 1500 r. With 225 r there is a gradual depression of leukocytes and platelets which reaches a low point about the 28th post-irradiation day. With larger doses the curve shifts to the left until, at 900 and 1500 r, bone marrow production appears to be almost completely interrupted and the subsequent depression in blood elements is consistent with the lifespan of these elements.

Of the blood elements, reticulocytes appear to be the most useful indicators of lethal doses of radiation. They are immature cells, recently produced by the marrow, and have a lifespan of about three days. Therefore, they are imminently capable of reflecting damage to the marrow. Studies of reticulocytes preclude the necessity of more cumbersome studies such as mitotic indices or radioiron studies to assess marrow function.

The patient with radiation sickness is analagous to the patient with a thermal burn. It is relatively unimportant to know that the burn was produced by steam, boiling water, flame or other agent. It is important to know the amount of functioning skin remaining. So it is with radiation sickness in which remaining marrow function determines survival in the early lethal range. Hematologic events are the best indicators of this function.

53. *Detection of the Small Left to Right Cardiac Shunt with Methyl Iodide-131.*

Faber F. McMullen, Jr., William C. Sutton, Herbert C. Allen, and Hugh H. Hanson (Department of Nuclear Medicine, Hermann Hospital, Houston, Texas)

Methyl iodide-131 has been applied practically for detection of left to right shunts in the cardiopulmonary laboratory of a general hospital. The method has proved useful because of the simplicity and accuracy in the detection of shunts not discernable by oxygen gradient method.

Methyl iodide-131 is available, relatively stable, safely stored, easily administered and detected. The gas is produced from locally obtained materials in an inexpensive generator and is replenished at three weeks intervals. The delivery apparatus consists of a delivery container, hood system, filter arrangement and evacuation pump.

The gas is delivered to the left atrium by inhalation and detected in the pulmonary artery or right heart chambers by aspirated sampling through a cardiac catheter. The samples are counted with a scintillation crystal.

The normal appearance time from the left atrium to the pulmonary artery or right side of the heart is 18 seconds; the appearance time in the presence of a left to right shunt is 5 seconds or less than 10 seconds.

The shunt is located anatomically by repeating inhalations and sampling in a retrograde fashion at the base of the pulmonary artery, infundibular chamber, right ventricle, right atrium and the superior and inferior vena cavae.

This procedure has been successfully employed since June 1960, and has proved to be safe, practical and reliable.

54. *A Simplified Method for Immuno-Assay of Human Serum Insulin Levels.*

Robert C. Meade (Wood Veterans Administration Hospital, Milwaukee)

The insulin immuno-assay technique of Yalow and Berson has been modified to permit assay of human insulin at normal concentrations using commercially available insulin I^{131} with specific activity of 1 to 5 mc/mg. Guinea pigs were injected with either human or beef-pork insulin and the antibody diluted to give the desired binding in the range of 2.5 to 250 microunits of insulin per ml of serum. Insulin I^{131} was added to serum to give concentrations of 0.1 to 0.2 mμg per ml. The insulin antibody was then added and the mixture incubated at 2-4° C. Two ml aliquots were then added to a test tube containing 200 mg of an anion exchange resin cycled to the hydroxide form. The activity of the sample was counted in a well counter. Serum and resin was mixed at 25° C for 2 hours and then the resin was washed three times with distilled water. The activity remaining bound to the resin was then counted

and calculated as a percent of the total activity. Standards consisted of human or commercial insulin diluted in 6% albumin to which insulin I^{131} and antibody were added and the procedure carried out as above for the serum. Serum insulin concentration was calculated from the standard curve. The method has been used to study serum insulin concentrations in response to glucose and oral hypoglycemic drugs in patients.

55. *Carrier Dose Effects Upon Blood Disappearance Rates of the I^{131}-Iodopyracet Radioisotope Renogram in Rabbits.* **O. M. Meredith, Jane Post, and John Holmes (Laboratory of Nuclear Medicine and Radiation Biology of the Department of Biophysics and Nuclear Medicine, School of Medicine, University of California, Los Angeles)**

Two methods lead to a greater understanding of the radioisotope renogram: (1) graphical estimation of exponential slopes of the external γ-ray scintillation recordings of the blood disappearance of I^{131}-iodopyracet, and (2) study of the effect of different carrier dose levels. (The graphical technique has been a regular tool of investigators in the study of liver blood flow and reticuloendothelial phagocytic response.) The advantage of this approach is that the physiological processes involved have been studied extensively already, with renal clearance measurements. Thus, opportunity exists to associate patterns of exponential slopes of conveniently obtained γ-ray scintillation records with features of the physiological response elucidated by clearance methods, and consequently, to improve understanding and interpretation of the externally observed blood disappearance curve.

When carrier dose levels of I^{131}-iodopyracet at 200 mg/kg or lower, were administered intravenously to Dutch rabbits, two exponential slopes of the blood disappearance curve were observed, a fast slope of 1-2 minutes half-time followed by a slower slope of 9-15 minutes half-time. At higher dose levels (circa 500 mg/kg) there was a definite change in the exponential slope pattern of the blood disappearance curves. Instead, a slow exponential slope of 30 minutes or greater preceded a faster slope of 9-15 minutes half-time. Preliminary studies have shown that the magnitude of the plasma level of I^{131}-iodopyracet at the high carrier dose level is constant in value (from animal to animal) for that instant when the blood disappearance slope changes from a slow to faster exponential process. This finding suggests that the tubular cells are saturated until the blood disappearance curve changes slope. The slow exponential slope may correspond to the rate of glomerular filtration only, and the faster one to the rates of tubular secretion plus glomerular filtration.

It appears that blood concentration occurring at the time when the blood disappearance curves change slope, corresponds to tubular saturation level described in renal clearance tests. Further studies are in progress to substantiate this conclusion.

56. *The Co^{60} Vitamin B_{12} Binding Capacity of Mature and Immature Leukocytes.* **Leo M. Meyer, Eugene P. Cronkite, Robert W. Bertcher, Inez F. Miller, Irving Jones, and Claire W. Mulzac (Department of Laboratories, South Nassau Communities Hospital, Oceanside, New York, and Medical Department, Brookhaven National Laboratory, Upton, New York)**

Leukocytes from normal subjects and from patients with a variety of hematologic disorders were harvested, concentrated and suspended in their own plasma. Total white blood cell estimates were made with the Coulter counter. An aliquot of each suspension was subjected to sonic oscillation until complete cellular destruction ensued. Co^{60} vitamin B_{12} binding capacity of plasma, intact and disintegrated white blood cells was determined, using incubation and exhaustive dialysis techniques. Values for plasma were subtracted and results adjusted for absolute counts of 100,000 intact leukocytes per mm^3.

Results show that intact mature granulocytes have the highest Co^{60} vitamin B_{12} binding capacity. Mixtures of mature and immature leukocytes from individuals with chronic my-

elocytic leukemia showed lower values, proportionate to the degree of immaturity. Cells from cases of acute myeloblastic leukemia came next in order. Lymphocytes, mature and immature, gave the lowest values, respectively. In most instances disintegrated cells had a higher radiovitamin binding capacity than the intact leukocytes.

Results will be discussed in relation to B_{12} serum binding studies in acute and chronic leukemia.

57. *Pernasal Transsphenoidal Yttrium-90 Hypophysectomy: Present Status.* Robert D. Moseley, Jr. and Paul V. Harper, Jr. (Departments of Radiology and Surgery, The University of Chicago, Chicago)

The results of hypophysectomy by means of implantation of radioactive yttrium in more than one hundred patients with metastatic neoplasm will be presented. Y^{90} oxide pellets are made by irradiation (n, γ) of Y^{89} oxide pellets. These 4 mg pellets will pass through a 17 gauge needle. Usually six such pellets, each with 1 mc Y^{90}, are placed within the hypophysis. As a result, an average of 150,000 rads are delivered. The technique of implantation under fluoroscopic control will be shown in a short movie. Of the more than 20 cases which have come to autopsy, the hypophyses average 90% destruction by this procedure. As with other types of hypophysectomy for hormonal dependent tumors, control of the tumor is successful in 20+% of treated cases.

58. *The Effect of Endotoxin on Hepatic Blood Flow.* John M. Moses, William J. MacIntyre, and Dieter Koch-Weser (Department of Medicine, Western Reserve University, Cleveland)

The hemodynamic alterations induced by endotoxin have been studied in dogs by several investigators. Hepatic congestion and pooling of blood in the portal system appear to play a crucial role in the reduction of venous return and cardiac output. Anatomical changes in the hepatic venous system consistent with circulatory alterations produced by endotoxin can be demonstrated after injections of other toxins in the dog but not in the rabbit. Furthermore, accelerated removal of endotoxin by the liver has been demonstrated in rabbits made "tolerant" by daily injections of sublethal amounts of endotoxin, and has been attributed primarily to enhanced reticuloendothelial activity. Experiments have been undertaken in our laboratory to define the relative roles of hepatic flow and reticuloendothelial uptake of endotoxin by the liver in tolerant rabbits. Flow has been measured by the clearance of radioactive gold colloid and the clearance of endotoxin has been determined following the injection of Cr^{51} labelled endotoxin. Disappearance curves under a variety of conditions have been obtained by continuously monitoring the radioactivity of the blood in a carotid artery-jugular vein shunt led through a 4 mm sidewell scintillation counter. The results suggest that enhanced clearance of endotoxin by tolerant rabbits may be influenced by alterations in hepatic flow.

59. *EDTA-Co "-Ray Carrier".* William G. Myers (Department of Medicine, The Ohio State University Health Center, Columbus)

To radioactive Cobalt-57 or Cobalt-58 solutions in small test tubes is added 1.0 ml of 0.010 M disodium ethylene-di-amine-tetra-acetate. One ml of 0.0010 M $CoCl_2$ carrier is added and the solution made weakly basic with dilute NaOH. Completeness of reaction is assured by dipping in water near boiling.

The chelated radiocobalt is firmly bound in the complex. Virtually no radioactivity remained in mice several hours after injection.

The complexes should find many applications as "γ-ray carriers" in Photon Projection Analysis for dynamic physiological studies of short duration, e.g., circulation time, cardiac output, myocardial blood flow, renal studies, etc.

The physical "shelf" half-lives of 72 days for the Co^{58} complex and 270 days for the Co^{57} complex make for convenience and economy. The biological half-lives are short and radiation exposures are low. The 123-kev and 137-kev γ-rays emitted by the Co^{57} chelate are useful when efficient shielding collimation is desirable and "narrow beam" attenuation of about 4.3 cm in soft tissues is adequate. The 0.81-Mev γ-ray and 0.51-Mev annihilation photons emitted by the Co^{58} complex are available when it is essential to have photons with half-thicknesses about twice as great. The Co^{60} chelate, with "shelf" half-life of 5.27 years, could be used for even greater penetration.

Toxicity of non-labeled EDTA-Co is low. All mice and rats survived intravenous injections with 100 milligrams of cobalt per kilogram of body weight in the chelated complex, much of which appears quickly in the urine.

60. *Radioiodine-125 for Clinical Photon Projection Analysis.* **WILLIAM G. MYERS and PRENTISS M. DETTMAN (Departments of Medicine and Surgery, The Ohio State University Health Center, Columbus)**

Radioiodine-125 is proving to be quite suitable for making "photonicons" of diseased thyroid glands. Displacement of normal thyroid tissue by tumors has been revealed by distorted distributions of I^{125} found after giving labeled iodide.

The detector consists of a NaI(Tl) crystal only 2 by 12.5 mm coupled to the ¾-inch multiplier phototube in a Nuclear-Chicago DS8 basic probe, to which a small brass collimator is attached. When mounted in the ½-inch thick lead carriage of our scanning machine, and with the spectrometer set to straddle the 27.4-35.4 kev I^{125} photons, the background is about ten counts per minute.

Calculations indicate the maximum radiation exposures involved, when I^{125} is used, are less than one-tenth as great as when I^{131} is used to make comparable photonicons.

Also, rates of uptake of I^{125} are assessed by repeatedly counting during a few hours with a detector placed over the thyroid gland. The NaI(Tl) crystal in this detector is 0.25 by 1.5 inch and the background, without shielding, is only about 17 counts per minute. Calculated radiation exposures involved in such studies with I^{125} are less than ten ergs per gram of gland.

The sevenfold longer half-life of I^{125}, and the ease of protection against the low energy photons emitted by it, are conveniences in comparison with past experiences with I^{131}.

The solutions are "purified by aging" to free them of any I^{124} and I^{126} present in them originally.

61. *Use of Neutron Activation Analysis for Studying Stable Iodide Uptake by the Thyroid.* **WIL B. NELP, HENRY N. WAGNER, JR., and JAMES H. DOWLING (Diagnostic Radioisotope Laboratory, Johns Hopkins Hospital, Baltimore, and Nuclear Medicine Branch, National Naval Medical Center, Bethesda)**

A technique of neutron activation analysis was developed to measure quantitatively the iodine content of biological fluids. Subjects were given tracer doses of I^{131} (2-4μc) or I^{132} (5-15μc). For the next 2 hours counts were made over the thyroid, and blood and urine were sampled. The urine was counted, passed over an ion exchange column to separate the stable iodide, which was quantitated by neutron activation to provide the specific activity. Then from counts of the blood samples and counts over the thyroid, the stable iodide accumulation rate of the gland was calculated. With this technique, it was possible to measure thyroidal uptake of iodide in micrograms per unit time, and to relate it to plasma inorganic iodide concentration.

In 34 euthyroid subjects, the uptake of stable iodide averaged 6.2 micrograms per 2 hours (range 1.4–20 μg). Plasma concentrations ranged from 1 to 10 micrograms per liter. Iodide uptake was greatest when plasma concentrations were highest. To study the effect of increased plasma iodide concentrations, euthyroid subjects were given increasing amounts of

oral iodide for periods as long as 47 days. The thyroid accumulated iodide at an increasing rate until the plasma iodide level reached 75 micrograms per liter. At greater plasma concentrations, the iodide accumulation fell, but remained several times higher than normal.

In euthyroid subjects subsequently given increasing amounts of dietary iodide the radioiodine uptake (percent dose per 2 hours) was initially 7.2 percent when corrected for neck extrathyroidal radioactivity by the perchlorate block method. Administration of iodide sufficient to increase plasma concentrations from 5 to 50 μgm per liter decreased radioiodine uptake 0.1 percent per microgram per liter increase in plasma concentration. At serum concentrations greater than 100 micrograms per liter the percent dose uptake decreased at a slower rate. Despite the decrease in radioiodine uptake, the thyroid continued to accumulate stable iodine at a rate six times normal value even after oral administration of iodine for one month.

62. *Measurement of Cerebral Circulation by External Collimation Following the Intravenous Injection of Radioisotope.* W. H. Oldendorf (Veterans Administration Center, Los Angeles)

A technique has been developed which compares simultaneously the blood flow in each cerebral hemisphere. The technique consists of the intravenous injection of 400 microcuries of I^{131} labelled hippuric acid by a method which results in a well demarcated bolus. About eight seconds later this material appears in the brain and the relative rates of build-up in each hemisphere are monitored for the next ten seconds. A series of normal controls with and without digital carotid compression suggests that this comparison of the upgoing slopes of the curves produced by a detection apparatus collimated to isolate the two hemispheres is a valid measure of relative blood flow to the hemispheres.

The test is extremely simple and painless to administer. The hippuric acid is almost entirely in the urinary bladder within an hour greatly reducing the radiation of the patient and allowing frequent test repetition. Some clinical evaluation has been carried out and suggests the test might be of value in certain situations resulting in a disparity of volume of circulation to the two hemispheres. The possibilities of obtaining a quantitative flow volume are discussed.

63. *The Topographic Distribution of Liver Metastases. Its Relation to Surgical and Isotope Diagnosis.* Ahsen Ozarda and John Pickren (Department of Nuclear Medicine, Rosewell Park Memorial Institute, Buffalo)

150 cases of liver metastases have been analyzed topographically in order to assess the value and limitation of isotopic liver scanning and to correlate the scanning results with the post mortem findings. Almost all cases which have been scanned at Rosewell Park Memorial Institute were examined at autopsy.

From this study we have learned that: 1) In approximately one-third of the cases of multiple liver metastases the organ was found to be normal in size. Therefore it should be emphasized that liver enlargement does not always accompany liver metastases. 2) More than 10% of the metastatic nodules were found to have no evidence of surface involvement. Therefore exploratory laparotomy is not reliable for a significant number of liver metastases. 3) There is an extreme limitation in the surgical approach to metastatic liver disease since less than 2% of the observed cases showed only single metastasis in one lobe. 4) A discrete, small space-occupying lesion which is smaller than 2 cm in diameter could not be accurately detected because of the limited resolution of the scanning devices available at that time.

64. *Site of Binding of Cr^{51} to Hemoglobin.* Howard A. Pearson (Department of Nuclear Medicine, U. S. Naval Hospital, Bethesda)

Cr^{51} tags the globin portion of the hemoglobin molecule; however, there are few studies concerning site of the chromate-hemoglobin bond. Globin consists of two pairs of polypeptide

chains called the alpha and beta chains. Hemoglobin A may be designated $\alpha_2\beta_2$. Most abnormal hemoglobins are altered only in β chains. Hgb. C can be designated as $\alpha_2\beta_2^C$. Hgb. H, however, contains no α chains. It is a tetramer of β chains only and has been designated, β_4.

Red cells from a patient with Hgb. H disease were labeled with Fe^{59} and Cr^{51}. Radioactive hemolysate was separated into H and A components by starch block electrophoresis. Hgb. H constituted 18% of Hgb. A. and 82% of the total hemoglobin. The Fe^{59} activity was similarly divided. However, when the fractions were analyzed for Cr^{51}, in the H fraction, accounting for only 18% of the total hemoglobin, about 34% of the Cr^{51} counts were found. Since Hgb. H contains twice as many β chains as Hgb. A, one explanation for the two-fold difference in Cr^{51} specific activity might be that isotope tags to the β chains only.

In acid solutions, there is asymmetric dissociation of the hemoglobin molecule into free α_2 and free β_2 units. When the solution is returned to neutral pH, α_2 and β_2 units recombine *randomly* to reform intact hemoglobin molecules. If a mixture of Cr^{51} tagged Hgb. A were mixed with nonradioactive Hgb. C and subjected to acid dissociation and recombination, two alternative results can be postulated.

If Cr^{51} tags only to β chains, after acid dissociation and recombination, no radioactive Hgb. C would be present in the recombination mixture. Since both radioactive and chemical markers are in the β units no interchange would occur. However, if Cr^{51} tags to both α_2 and β_2 units, after acid dissociation and recombination, a new hybrid, radioactive Hgb. C, would be formed.

Hgb. A from a normal person was mixed with Hgb. C and subjected to acid dissociation and recombination. No significant increase in radioactivity of the Hgb. C was seen after recombination, confirming chain binding.

Thus, by two different techniques it has been demonstrated that the Cr^{51} tags largely to β chains. This is of interest, first, because it suggests a unique property or relationship of the β chain—not shared by the α chains. Secondly, since the tag remains with the β chain during recombination experiments, this may offer a simple tool for identifying the abnormal polypeptide chains of hemoglobin variants.

65. *Analysis of the Radioactive Renogram Curve by an In Vitro Experiment.*

Felix J. Pircher, Audrey V. Wegst, and Vernon N. Dodson (Radioisotope Unit, University of Michigan Medical Center, Ann Arbor)

The technique of radioactive renography uses scintillation detectors to record the rate of tubular secretion of an intravenously injected radioiodinated contrast medium independently for each kidney. The technique produces a curve in which every point represents count rate versus time; it is characteristic for renal activity. The "normal" curve has an ascending slope, a peak, and a descending slope. The slopes have exponential characteristics and are in principle defined by half-time of count rate increase, half-time of count rate decrease, by the maximum count and by the time at which the maximum count occurs. These four parameters determine the curve and can be measured. For the interpretation of the test, it is essential to know the factors that determine the magnitude of these parameters. The purpose of this study was to determine these factors and the mode of their effect upon the parameters of the curve. Theoretical considerations have led us to construct a model which simulates the physiological situation in a radioactive renogram test. The model consisted of an open two compartment system in which a radioisotope dilution was exchanged at a certain rate.

Several experimental runs were made while the activity in one compartment was measured in counts per minute by a scintillation detector connected to a rate meter and recorded by a rectolinear recorder. The following components were varied: 1) The flow rate; 2) The volume of compartment one; 3) The volume of compartment two. In the curves so obtained the following parameters were measured: 1) Half-time of ascending part; 2) Half-time of descending part; 3) Maximum count; and 4) Time at which maximum count occurred.

The results indicate that the flow rate, the kidney volume, and a fraction of the blood volume are the main contributing factors which determine the renogram curve. In addition,

good correlation was found between these results and the equations of a mathematical model of this open two-compartment system. It would appear that these results might lead to a more factual interpretation of the radioactive renogram.

66. *On the Mechanism of Action of Thyrotropin on the Thyroid.* **JAMES A. PITTMANN, JR., DON HAMNER, and BERNARD H. WILLIAMS (Veterans Administration Hospital, and Dept. of Med., Univ. of Ala. Med. Center, Birmingham)**

Thyrotropin (TSH) stimulates oxidation of C^{14}-labeled glucose to $C^{14}O_2$ by thyroid slices. This effect occurs quite early (less than 5 min.) suggesting that it is important in the activation of thyroidal hormone synthesis. In order to test the postulate that TSH acts primarily on the pentose phosphate pathway, we have incubated thyroid slices with sodium pyruvate-2-C^{14} in phosphate buffer with varying concentrations of fluoride to inhibit enolase activity and block the glycolytic route to that pathway. TSH stimulates pyruvate oxidation markedly in the absence of fluoride. Stimulation is still evident in the presence of 10^{-4} and 10^{-3} M fluoride, and usually with 10^{-2} M fluoride. The completeness of the block is being evaluated at present. Stimulation has not been obtained in cell-free preparations. It has been reported that (1) vasopressin (ADH) can stimulate the thyroid, (2) ADH may act on the kidney by a thiol-disulfide reaction, (3) cysteine is the most abundant amino acid in TSH. Although 10^{-2} M cysteine is stimulatory, ADH is inert in this system, neither stimulating nor inhibiting TSH stimulation. TSH is bound to thyroid slices after brief exposure, and the possible role of sulfur-sulfur interaction in this binding is being studied.

67. *Biochemical Studies on the T-3 RBC Uptake.* **JOSEPH L. RABINOWITZ (Radioisotope Service, Veterans Administration Hospital, Philadelphia)**

Since Hamolsky and his group arrived at a practical measurement of thyroid function by use of the uptake of T-3 by RBCs, it has been the aim of this and other laboratories to correlate the limits of usefulness for the test and try to explain its biochemical significance. The exchange of washed RBCs from one individual with those of another did not effect the results of the test. This exchange includes mixing RBCs of different species, i.e., mice, sheep, etc., without significantly affecting results. It is thus suggested, that the RBCs are only indicators and will absorb all available free T-3. Therefore, it should be possible to perform the same test by separation of protein-bound T-3 from free T-3 by resin or other means without the use of RBCs as indicators. Unfortunately, when the test was performed in this manner, the numerical percentage error became larger, (the value obtained was the difference of the uptake and 100). Thus, a 20% uptake by RBC T-3 shows an experimental error of ± 3. For the 80% value determined for protein-bound T-3, the error was ± 12, rendering the test less reliable. It is possible to have maximum T-3 binding in less than 20 minutes, but measurement of unbound T-3 on RBCs required over 2 hours for Freundlich isothermal equilibrium. Work continues in attempts to simplify the length and complexity of the test by determination of the sera-bound-T-3. The clinical significance of this test is not discussed.

68. *Validity of Measurement of Hepatic Blood Flow by Colloidal Clearance Methods.* **MOHAMED A. RAZZAK and HENRY N. WAGNER, JR. (Diagnostic Radioisotope Laboratory, Johns Hopkins Hospital, Baltimore)**

Our attempts to use colloidal clearance techniques to measure hepatic blood flow (HBF) in man by means of a radiation detector over the thigh, precordium or face were unsatisfactory, since the clearance rate was a complex exponential function. In contrast, when activity of serial blood samples was measured, the clearance rate was a single exponential function for 20 minutes. Moreover, the clearance rate in both man and dog was reproducible and independent of the number of particles injected.

To test the validity of the colloidal clearance technique, HBF was measured simultaneously by Blalock's collection method. The advantages of this method are its reproducibility and the ability to obtain mixed hepatic venous samples for estimation of hepatic extraction ratios. In the dog, HBF increased linearly with weight. The relationship between the clearance method using silver coated gold particles and the collection method was: HBF (collection) equals 0.98 HBF (clearance) plus 58 ml/min. When corrected for simultaneously measured extraction ratios, the two methods gave nearly identical results. The mean extraction ratio of numerous particle lots was 64 ± 11% (S.D.) and fell slowly with time. Epinephrine decreased the hepatic extraction ratio by one-fourth, necessitating simultaneous determination of extraction ratios in studies of the effect of the drug on hepatic blood flow.

69. *The Measurement of Total Body Potassium in Man and its Relation to Gross Body Composition.* Alexander P. Remenchik and Charles E. Miller (Veterans Administration Hospital, Hines, Illinois)

This study was designed to delineate the degree of precision of the estimation of total body potassium in man and to relate the estimation to the lean body mass of man. Total body potassium was estimated by the measurement of K^{40} activity in the whole body scintillation counter and by the measurement of total exchangeable potassium (K_e) using K^{42}. Lean body mass was calculated from the measurement of tritiated water space (TBW). The subjects were clinically well ambulatory hospital patients. The mean difference in 5 subjects between measurements of K_e, one week apart, is 2.4 ± 0.7%. The mean difference between measurements of TBW in 6 subjects, done on the same day, is 1.3 ± 0.3%. The mean K_e/K_{40} ratio is 89 ± 1.3% in 15 subjects. The lean body mass content of potassium is 2.12 ± 0.06 Gm/kg in 12 subjects (from K_e) and is 2.39 ± 0.04 Gm/kg (from K^{40}) in 14 subjects. The gross body content of potassium is 1.69 ± 0.05 Gm/kg (from K_e) in 20 subjects and is 2.05 ± 0.07 Gm/kg (from K^{40}) in 18 subjects. The mean body fat content is 17.5 ± 2.3% in 17 subjects. These data suggest that all of the potassium in man is not exchangeable. These estimates of the lean body mass content of potassium was lower than the values reported by others but agree with their data expressed in terms of gross body weight. Our estimates of body fat agree with values reported by other investigators.

70. *Intracavitary Radioactive Colloidal Gold: Results in 257 Patients.* Raymond G. Rose (M. D. Anderson Hospital & Tumor Institute, Houston)

During the eight-year period from April 1952 to March 1960, a total of 257 patients received 322 intracavitary instillations of radioactive gold at the M. D. Anderson Hospital and Tumor Institute. Included are: 207 patients referred for palliation of malignant effusions (126 peritoneal, 85 pleural and one pericardial application); 9 patients treated to prevent development of ascites; 26 patients receiving Au^{198} as prophylaxis after intraperitoneal spillage of the cancer; and 15 patients treated for multiple peritoneal implants. Sixty-five per cent of patients with pleural effusions and fifty-seven per cent of patients with ascites benefited from the radiogold therapy. Of the nine patients treated to prevent ascites, none developed fluid. Of special interest are the groups where Au^{198} was given with curative intent: 20 of the 26 patients treated for carcinoma spillage are alive and well, with three of the patients now followed for more than five years; 6 of the 15 patients treated for diffuse peritoneal implants remain well, two others died of unrelated disease two and six years after Au^{198} therapy, with no evidence of tumor found post-mortem.

Complications of therapy and their prevention are discussed, along with current concepts of the status of intracavitary radioisotopes in the management of disseminated carcinoma.

71. ***Review of Studies of the Removal of Fission Products From Man.*** **BETTY ROSOFF and HERTA SPENCER (Division of Neoplastic Diseases, Montefiore Hospital, New York)**

Stimulated by the observation that different rare earth chelates of the polyamino-acid type are almost quantitatively excreted, the effect of the chelating agents ethylenediaminetetraacetic acid (EDTA) and diethylenetriaminepentaacetic acid (DTPA) was studied on the removal of radioactive yttrium, lanthanum and scandium. Y^{90} or Sc^{46} were injected as the weak chelate agent nitrilotriacetate (NTA), and 24 hours later infusions of either 0.5 gm, 1 gm or 2 gm of Ca-DTPA were administered intravenously on several days. The urinary excretion of Y^{90} increased 5 to 10 times over the baseline excretion; the Sc^{46} excretion was enhanced 20 times. Ca-DTPA proved to be more effective in comparison to equivalent amounts of Ca-EDTA. Studies of the removal of Sc^{46} by Ca-DTPA 5 days after the Sc^{46} injection revealed effective enhancement of the Sc^{46} excretion. In studies carried out with Zn^{65}, Ca-DTPA again proved to be the agent of choice and enhancement of Zn^{65} excretion was still possible after 100 days. Since Ca-DTPA and Ca-EDTA given in amounts up to 2 gm are relatively non-toxic, the practical application of these chelates in fission product removal from man are discussed.

72. ***Strontium-85 as a Tracer for Calcium in Man.*** **JOSEPH SAMACHSON and HERTA SPENCER (Division of Neoplastic Diseases, Montefiore Hospital, New York)**

Because strontium follows the same metabolic pathways as calcium in the human body, Sr^{85} has been used for such purposes as calculating the accretion of bone mineral and estimating endogenous fecal calcium. The quantitative differences between the two elements, however, are sometimes striking and the usefulness of Sr^{85} as a tracer for calcium will therefore vary according to the individual, the parameter studied and the conditions of study. For instance, the relative absorption of Ca^{45} compared to Sr^{85} has been found to vary by a factor ranging from 1.35 to 3.70 and the relative retention 12 days after an intravenous dose, by a factor ranging from 1.35 to 2.5. The renal clearance of Sr^{85} may exceed that of calcium by a factor ranging from 2.5 to 6, the gastrointestinal clearance varying from 1.2:1 to 2.1:1. Those patients with the greatest variation of clearance ratios have the least variation of retention ratios. Plasma proteins bind Ca^{45} to a greater extent than Sr^{85}, and Ca^{45} appears to filter somewhat more readily through body membranes. Sr^{85} is a fairly good tracer for Ca^{45} in estimating partition between bone and soft tissue but even here, the relative values vary from one individual to the next. Ca^{45} usually, but not always, enters bone preferentially. Therefore, Sr^{85} is useful as a qualitative tracer for calcium but if quantitative conclusions are sought, the overall picture of retention and excretion must be taken into account.

73. ***Estimation of Fat Absorption by Monitoring of Expired Radioactive Carbon Dioxide.*** **A. D. SCHWABE, F. J. COZZETTO, S. M. MELLINKOFF, and L. R. BENNETT (Gastroenterology and Radioisotope Services, UCLA School of Medicine, Los Angeles)**

A rapid quantitative test for the diagnosis of steatorrhea based on the oxidative decarboxylation of C^{14} carboxyl labelled octanoic acid has been explored. Octanoic acid which is absorbed directly into the portal venous system and rapidly oxidized is a convenient fatty acid substrate. C^{14} octanoic has been used as the free acid or the triglyceride. Measurements of $C^{14}O_2$ have been made by the method of Tolbert, using an ionization chamber and vibrating reed electrometer. The entire test can be performed, using 2 microcurie doses, in less than one hour. Results with steatorrheas of various causes presently seem to indicate that a clear separation of patients with steatorrhea from normals is possible with this method.

74. *Radioiron Studies in the Investigation of Polycythemia Vera.* **W. John Simpson and Marc C. Bertrand (Ontario Cancer Institute, Toronto)**

Reports on radioiron studies in polycythemia vera have been infrequent, but have indicated a rapid plasma clearance and increased iron turnover rates. Since rapid plasma iron clearance is most commonly encountered with anemia, it was decided to explore the usefulness of this test in the differential diagnosis of primary and secondary polycythemia. In addition, the distribution of radioiron, demonstrated by total body scanning, was also to be studied, since the occurrence of extramedullary hematopoiesis may complicate the management of polycythemia vera.

To this end, 30 patients suffering from polycythemia vera have been studied in respect to plasma clearance rates and sites of localization of the radioactivity. The results will be compared with the findings in hematologically normal control patients, and polycythemia secondary to other disease processes. The total body scans will be correlated with bone marrow aspiration examinations. Some unusual findings in the total body scans suggest that these may be of value in the assessment of more advanced cases.

75. *The Effect of Various Agents on the Removal of Radiostrontium From Man.* **Herta Spencer and Joseph Samachson (Division of Neoplastic Diseases, Montefiore Hospital, New York)**

Since a qualitative relationship was noted between the urinary excretion of calcium and radiostrontium, enhancement of the calciuria was induced to promote the removal of radiostrontium from man. Tracer doses of Sr^{85} were given intravenously and the plasma levels and urinary and fecal excretion of Sr^{85} were determined for approximately 20 days. A second tracer was given during the administration of the enhancing agents and the same determinations were performed. Intravenously administered calcium, orally administered ammonium chloride, a combination of both these agents, intravenously administered stable strontium and the chelating agent, bis (2-aminoethyl) ether tetraacetic acid (BAETA), were found to increase the Sr^{85} excretion two to five times when given at the time of the injection of the Sr^{85} tracer. Each of these agents was also shown to be effective in removal of Sr^{85} as late as two weeks after exposure, in most instances to an extent comparable to that of the early removal, taking into consideration the percentage of Sr^{85} excretion in urine and stool before the enhancing agent was administered in this late phase.

76. *The Use of Triiodo-Thyroproprionic Acid (Triopron) in the Therapy of Hypothyroidism.* **Maxwell Spring (Bronx Hospital, New York)**

Triiodo-Thyroproprionic acid is one of the thyroxine analogues formed by removing one atom of iodine from the parent substance and substituting proprionic acid for alanine by deamination. Physiologically it has about 10% of the calorigenic and 28% of the antigoiterogenic activity of l-thyroxine and can depress cholesterol in non calorigenic doses.

The therapeutic effect of this drug was evaluated clinically in ten patients with hypothyroidism of various etiologies. All were females aged 26 to 61. Mean age was 53. None had cardiac symptoms. In the six patients who had electrocardiograms taken, the findings were typical of hypothyroidism. For the first few weeks the patients were seen at either weekly or biweekly intervals and monthly thereafter. Blood cholesterol and PBI determinations were made periodically. Electrocardiograms were made initially and then weekly until they were normal.

The initial dosage of the drug was one milligram daily. This was increased by one milligram at weekly intervals until a maximum clinical effect was obtained. Basal metabolic rates were so variable that they were discarded.

Improvement of symptoms began during the first week of therapy and reached a maximum clinically in eight patients after a daily dose of three milligrams had been given. One required

4.5 milligrams and another six milligrams for a similar effect. The electrocardiogram became normal after the daily dose was raised to two milligrams. The fall in cholesterol was variable with the doses of Triopron used. It consistently fell toward normal when the initial reading was high. There were no toxic effects.

Triopron was found to be an effective drug in the treatment of hypothyroidism.

77. *Comparison of Triiodothyronine and Potassium Iodide as Thyroid Suppressive Agents.* MAXWELL SPRING (City Hospital, Elmhurst, New York)

Triiodothyronine and potassium iodide were compared as thyroid suppressive agents. Both drugs were used in the same patient and he served as his own control.

Sixteen euthyroid patients (15 F, 1 M; age 15-69) and 16 hyperthyroid patients (15 F, 1 M; age 16-71) were studied. In some of the latter group, a suppression test was performed prior to radioiodine therapy. All of the euthyroid and 15 of the hyperthyroid patients completed both tests. There were 23 trials in the hyperthyroids and 18 trials in the euthyroids.

Method: 1) Control radioiodine uptake. 2) Triiodothyronine 25 μg t.i.d. for seven days. 3) Radioiodine uptake. 4) Wait two weeks. 5) Potassium iodide 100 mg in water, per os. 6) Seventy-two hours later radioiodine uptake.

Both drugs cause suppression of varying degrees in practically all the patients. Suppression is greater in euthyroid than in hyperthyroid patients. Potassium iodide administered in this fashion appears to be more or equally as suppressive as triiodothyronine in the majority of the hyperthyroid patients, before or after therapy, and in the majority of the euthyroid patients. Potassium iodide is far cheaper and better controlled than triiodothyronine as a suppressive agent.

78. *Radioisotope Techniques in Microbiology.* JOSEPH STERNBERG (Institute of Microbiology and Hygiene, University of Montreal, Montreal)

Microbes can be labeled by: 1) uptake of a labeled constituent added to the culture medium, or 2) physico-chemical addition of the isotope to a susupension of already grown cells. The uptake procedure employs usually microbial metabolites ($P^{32}O_4$, $S^{35}O_4$, C^{14} compounds, Fe^{59}, Co^{60}, etc.), although in some cases some periodic relatives non-metabolites (Se^{75} instead of S^{35}) could be taken up by a non-discriminating microbial cell.

The physical half-life of the isotope must match the growth curve of the microbe, and also the radioactive material must not induce radiation damage to the cell (over 10 microcuries/ml for P^{32} in some cases). In microbes labeled with P^{32}, the mutations induced by the transmutation of the incorporated P^{32} (P^{32}—S^{32}) must be also taken into consideration.

The *in vitro* labeling of suspensions of grown cells is done usually with I^{131} or Cr^{51}; the iodination or chromation of the microbe does not differ basically from that of any other compound containing proteins (for $Cr^{51}Cl_3$ and I^{131}) or unsaturated fatty acids (for I^{131}); a far larger amount of radioactive material can be added, since the radiation damage is reduced considerably; however, there is danger of an uneven labeling of the suspended cells, and also of a chemical damage of the microbe, due to the antiseptic properties of Iodine or Chromium, or other chemicals added during the iodination process.

When labeled microbes are used for further *in vivo* studies, their exchange reactions with the environing medium must be carefully assessed; in this case, it is advantageous to label complex constituents than simple ones, more rapidly exchangeable (e.g. tritiated thymidine instead of tritiated water).

Doubly and even triply labeled microbes can diminish the danger of misinterpretation due to exchange reactions.

79. *The "In Vitro" Uptake of C^{14}-Labeled Cholesterol by Red Blood Cells.*

JOSEPH STERNBERG (University of Montreal, Montreal, Canada)

The well-known property of red cells to exchange "in vitro" with water soluble compounds (P^{32}, Cr^{51}, Triiodothyronine-I^{131}) has been used in the study of the exchange between lipidic constituents of serum and red cells.

A solution of β lipoprotein is obtained from homologous serum by phenol precipitation and redissolution into saline. Various labeled lipid-soluble compounds (C^{14}-labeled cholesterol, C^{14}-labeled α tocopherol, steroids, P^{32}-labeled phospholipids) have been added to the lipoprotein solution. The thus enriched solution is clear and remains stable for at least 4 weeks at +4°C. The optimum addition of labeled cholesterol was in a proportion of 10-14% of the total cholesterol content of the lipoprotein.

Labeled lipoprotein (0.10 to 0.25 ml containing 160 to 400 μgm cholesterol) are added to 3 ml oxalated blood and incubated under continuous stirring in a water bath at 37°C. The blood is then centrifuged and washed twice with saline, the red cells are hemolyzed with distilled water, and the ghosts are centrifuged from the hemolyzate. The activity of all fractions is measured in a proportional counter and the results are expressed as per 100% hematocrit.

The red cell uptake averages 30-35% in control male subjects and 40-45% in control women. The labeled cholesterol is bound in a significant proportion to the ghosts: in males an average of 25-35%; in women 40-50%. This constitutes an important difference from the uptake of TIT^{131}, where only a fraction of 3-5% is bound to the ghosts. In rat, the uptake is higher (55-60%), but the ghosts are far less active than in man and guinea pig—3-5% of the total. There seems to be a parallelism between TIT uptake and cholesterol uptake of red cells, for in a group of maternal and fetal blood samples, the TIT^{131} as well as the cholesterol uptake of maternal red cells was considerably lower than that of fetal red cells. There does not seem to be a straight relationship between the lipoproteic pattern or serum cholesterol level and the red cell uptake of C^{14}-labeled cholesterol, but in some cases of hypercholesterolemic patients the red cell uptake is significantly lower (16-20%). Also, a lower uptake was found in jaundice, and a higher uptake in pregnancy. Rats treated with high amounts of α tocopherol or corn oil do not show a different uptake.

Work is in progress on a series of normal subjects and patients with disturbances of lipid metabolism to determine if this test has value in the diagnosis or prognosis of atherosclerotic diseases.

80. *Radiobiology.*

R. L. STRAUBE (Division of Biological and Medical Research, Argonne National Laboratory, Lemont, Illinois)

The effects of ionizing radiation have often been discussed in terms of cellular depletion resulting from cell death and mitotic block. However, these factors, although necessary are not sufficient to explain the changes incident to ionizing radiation. Cell depletion, as the result of primary destruction coupled with secondary loss from mitotic inhibition is but one side of the coin; it is not alone the number of cells killed, but, more importantly, which cells survive irradiation and what the potentialities of these cells may be. The continued existence of even a small number of relatively undifferentiated, multipotent cells, is of inestimably greater importance to the ultimate survival of the organism than the sparing of a much greater number of functionally active, mature cellular elements. The implications of interactions among surviving cells and their milieu are discussed in terms of both the immediate and delayed effects of radiation as seen in the whole animal. In addition the concept of radiosensitivity and the various factors that contribute to it are discussed.

81. *Twelve Years Experience With 7000 Rep as the Therapeutic Dose for Thyrotoxicosis.* **WILLIAM C. SUTTON and HERBERT C. ALLEN, JR. (Department of Nuclear Medicine, Hermann Hospital, Houston)**

The authors present experience gained in I^{131} therapy of thyrotoxicosis in 500 cases over a 12 year period. Various facets of I^{131} therapy are discussed.

The 7000 rep, (single-dose) therapy technique is presented with particular emphasis on pre- and post-therapy calculation of thyroid gland weight from an empirical formula and measurement of effective half-life.

Almost all patients received a standard tissue dose of 7000 rep in accordance with a prescribed protocol established in 1949. Those who became hypothyroid or who continued to demonstrate toxicity following the initial dose were classified as failures.

Utilization of a standard approach has enabled the authors to observe the course and results of I^{131} with a minimum of variables to evaluate.

Concepts have arisen during the period of observation which suggest that the standard 7000 rep tissue dose should be altered in certain groups of patients in whom tissue sensitivity may differ. Specifically, tissue sensitivity apparently varies with age, sex, prior surgery, and prior therapy with anti-thyroid drugs.

Results of therapy in the 500 cases are presented.

82. *Colloidal Suspensions of Human Albumen I^{131}* **(Tracer Techniques for Estimating Functional Abnormalities of the Reticuloendothial System (RES)).** **G. V. TAPLIN, E. K. DORE, and D. E. JOHNSON (Laboratory of Nuclear Medicine and Radiation Biology of the Department of Biophysics and Nuclear Medicine, and the Departments of Radiology and Medicine, School of Medicine, University of California, and the Los Angeles County Harbor General Hospital, Torrance, California)**

The role of the RES in man remains obscure after more than 50 years of extensive investigation largely for lack of an agent suitable for testing both the phagocytic and digestive functions repeatedly without danger either from sensitivity reactions or from false results caused by its storage in the RE cells. A simple, reproducible method for preparing sterile colloidal suspensions of human albumen I^{131} with small particle size (about 10 millimicrons) will be described. After intravenous injection, the particles accumulate rapidly in the von Kuppfer cells of the liver and disappear from the blood with a $T^{1/2}$ of about 3.5 minutes. The slightly denatured protein is then digested, presumably by enzymatic action, and free inorganic I^{131} is released into the general circulation. With the thyroid blocked, about 50 per cent of the I^{131} is excreted in the urine within 24 hours.

Tracer amounts (less than 0.1 mg/kg) are used to estimate liver blood flow, from blood disappearance and liver (von Kuppfer cell) accumulation rates by external scintillation counting-recording techniques. Two functions of the RES can *then* be measured when loading doses (2.5-5.0 mg/kg) of nonradioactive colloidal albumen are administered immediately before injection of the tagged material. The rates of blood disappearance and of I^{131} *release* from the liver ($T^{1/2}$ values in minutes) are indices of phagocytic and digestive capacities of the von Kuppfer cells respectively. The test procedure gives about 200 times less radiation exposure to the liver than an equal dose (10 μc) of radiogold.

Findings from more than 100 patients show that these indices may have great value in clarifying the role of the RES in resistance to infectious and toxic agents; in diseases involving this system; and as means for measuring the depressant action of certain steroid hormones (cortisone) and the stimulatory action of various materials (pyrogens) suspected of having these effects on RES functions.

83. *Heat Denatured Colloidal Suspension of RISA: Simplified Method of Preparation.* **G. V. Taplin, M. L. Griswold, E. K. Dore (Department of Biophysics and Nuclear Medicine, and the Departments of Radiology and Medicine, School of Medicine, University of California and the Los Angeles County Harbor General Hospital, Torrance, California)**

The preparation of heat denatured colloidal aggregates of human albumen labeled with I^{131} was initially described by Benacerraf and Halpern (1954) to measure liver blood flow and phagocytic function of the RE cells of the liver. Their method of preparation required about 30 steps beginning with heat denaturation, subsequent extraction and purification of the aggregates by multiple washings and centrifugations followed by radioiodination and final dialysis to remove excess I^{131}. The only reports of its use are those of the original authors, largely because the material has not been made available from radiopharmaceutical companies.

Colloidal aggregates of albumen may be prepared directly from commercially available RISA, thereby eliminating the tagging and dialysis procedures. Benacerraf's original denaturing procedure was followed initially and gave a yield of only 50 $\pm$ 10%. Of numerous methods employed to increase the yield, upward adjustment of pH prior to heating gave the best results with a consistent yield of 80 $\pm$ 5%. Suspensions produced by these modifications have nearly identical physical and physiological properties to Benacerraf's original material. The present procedure may be performed in any clinical laboratory and requires only two hours time of one technician.

The size of the suspended particles is about 10 millimicrons, based on half time values for their blood disappearance which are nearly identical with those for colloidal radiogold. The latter is known to have this size from direct electron microscopy measurements. Moreover the aggregates have a narrow range of size distribution from ultracentrifugation studies which also indicate that the molecular weight is approximately 400,000 to 500,000 or that each aggregate is composed of 6 to 7 albumen molecules.

Details of the simplified method are presented along with data showing its reproducibility. Results of liver blood flow measurements using colloidal radiogold in comparison with heat denatured RISA are presented to demonstrate the reliability and superiority of the new preparation.

84. *Quantitation of Menstrual Blood Loss—Development of a Simple, Accurate Method.* **W. Newlon Tauxe (Section of Clinical Pathology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota)**

Clinically, quantitation of menstrual blood loss is often desired by the gynecologist, perhaps more often by the hematologist.

Exact measurements of radioactive isotope labeled blood are difficult due to the irregularity of the counting source, necessitating other measures which are often offensive to esthetic sensibilities or too patently inaccurate to be worth the effort.

We have developed a method of counting menstrual pads which has proved highly accurate and simple.

A few days before the onset of menses the patient's blood is labeled with Cr^{51}. Peripheral blood is withdrawn through the menstrual period to obtain counting standards. Usually red cell survival and gastro-intestinal blood loss determinations are made simultaneously.

Basically we have determined the shape of an iso-sensitivity plane over a NaI(Tl)

scintillation crystal, and fashioned a lucite counting dome to these dimensions. Over this dome, irregular counting sources such as menstrual pads may be counted with accuracy.

85. *The Value of the Plasma Iron Turnover in the Differential Diagnosis of the Polycythemias.* NANCY TELFER, NORMAN L. SCHIFFMAN, and FRANZ K. BAUER (Department of Medicine, Los Angeles County Hospital and University of Southern California School of Medicine, Los Angeles)

Of the three recognized types of polycythemia, relative polycythemia can be differentiated from primary and secondary polycythemia by a blood volume determination.

The plasma iron turnover can be used to differentiate between primary and secondary polycythemia and is of special value in cases in which other tests such as arterial oxygen saturation, pulmonary function studies, and bone marrow examinations are equivocal.

It has been shown that patients with secondary polycythemia have a plasma iron turnover that is much greater than normal, but is commensurate with the increased red blood cell mass, while patients with primary polycythemia have a plasma iron turnover which is greater than necessary to maintain the increased red blood cell mass.

A method of measuring the plasma iron turnover using a serum iron determination, the iron clearance half-time and the plasma volume with the same tracer dose of Fe^{59} is reported. There is minimal handling of blood.

A simple proportion was used to determine the predicted plasma iron turnover (PIT) for the patient's red blood cell mass.

$$\frac{\text{PIT (Predicted) } (\times)}{\text{PIT (Normal)}} = \frac{\text{Patient's RBC mass}}{\text{Predicted RBC mass based on height and weight}}$$

Results: The ratio of the Patient's PIT to Predicted PIT in 5 control subjects ranged from 0.67 to 1.10 (mean 0.84); in 3 patients with relative polycythemia from 0.81 to 1.04 (mean 0.94); and in 4 patients with secondary polycythemia from 0.90 to 1.21 (mean 1.07). There is no significant difference among these 3 groups.

However, in the patients with primary polycythemia, the ratio of Patient's PIT to Predicted PIT was 1.5 to 5.7 (mean 2.6). These values are significant when compared to the control values, ($0.02 < p < 0.05$).

86. *A Course in Radioisotopes Presented for Pharmacy and Medical Residents and Technicians.* MANUEL TUBIS (Veterans Administration Center, and the Department of Radiology, University of California Medical Center, Los Angeles)

This course was designed to provide a review of the required basic nuclear chemistry and physics, radioisotope methodology and techniques, instrumentation, health physics, the procurement and dispensing of radioactive materials. General and specific information was provided for the applications to hospital pharmacy, pharmaceutical practice and research and the probable role of hospital pharmacists in the nuclear age. Specific topics covered were incompatibilities, handling and storage problems, dosage forms, drugs for radiation sickness and the role of the pharmacist as a source of information to the allied professions, etc. The course also provided some training for the requirements for the "Byproducts Material License" and basic fundamentals for technicians. Audiovisual aids and demonstrations supplemented the course.

87. *Regulation of Red Cell Production by Erythropoietin.* **DONALD VAN DYKE and JOHN H. LAWRENCE (Donner Laboratory and Lawrence Radiation Laboratory, University of California, Berkeley)**

Although the use of Fe^{59} has increased the sensitivity of assay methods for erythropoietic hormone, it is still not possible to demonstrate convincingly the presence of this hormone in normal animals or human beings or in conditions of mild hematological stress. High titers of erythropoietin have been demonstrated in patients with severe hematological disorders or in animals under nearly lethal hematological stress. Assays of plasma and urine from otherwise "normal" human beings with severe iron deficiency anemia secondary to hookworm infestation or to chronic blood loss show elevated titers of erythropoietin only with hemoglobin concentration below 5 grams per 100 ml. The abruptness with which the titer rises and the severity of the anemia required before measurable titers appear are similar in man and in rabbits, sheep and dogs. The fact that no measurable erythropoietin titer can be demonstrated when hemoglobin concentration is well below that required for intense stimulation of erythropoiesis and the abruptness of the rise at hemoglobin concentration of 4 Gm% or less suggests that erythropoietin may not be an important factor in the control of erythropoiesis except in extreme circumstances or may be the result of the insensitivity of present assay methods.

88. *Acid Quenching in Liquid Scintillation Assay of Tritium.* **ROGER VEATCH and I. GORDON FELS (Radioisotope Service, Veterans Administration Hospital, Hines, Illinois)**

The spectral effects of hydrochloric, sulfuric and phosphoric acids upon phosphor performance were examined in a liquid scintillation medium for tritium assay. Comparison of the absorbance results obtained with these acids with their quenching effects reveals that absorbance intensity is roughly proportional to the degree of quenching of tritium counting at similar concentrations. Also, counting data obtained for hydrochloric and sulfuric acids over a wide range of concentrations demonstrate that the acids differ in their quenching effect according to their degree of hydrogen ionization. Evidence is presented to demonstrate that the hydrogen ion contributed by the acid to the scintillation medium causes oxonium and ammonium salt formation with the oxazole phosphors, and thereby reduces the counting efficiency. In summary, the following favorable evidence may be cited: 1) The secondary phosphor, POPOP, with capacity for forming a double oxonium and ammonium salt, absorbs energy more markedly in acid than the primary phosphor, PPO, which can form only a single oxonium and ammonium salt. 2) Enhanced spectral absorption of the phosphors in acid is consistent with the absorption observed with chromophores following salt formation. 3) When alkali is used with the phosphors instead of acid, no quenching is observed. 4) A close relationship exists between the degree of quenching and the hydrogen ion concentration.

89. *Radioisotope Renograms with 2, 6-Diiodosulfanilate-I^{131} as a Test Agent.* **CHESTER C. WINTER and WILLIAM G. MYERS (Departments of Urology and Medicine, The Ohio State University Health Center, Columbus)**

This compound was first shown to be excreted exclusively by the kidneys in animals and in human beings in 1957 by the co-author. It is easily and quickly labeled with I^{131} in our laboratory.

It is found to be satisfactory for making radioisotope renograms in patients with normal and abnormal kidney function.

High rates of excretion are demonstrated in 30-minute urine samples, with correspondingly short biological half-lives. It does not appear to be metabolized by the liver or thyroid gland.

Its stability, ease of preparation, and low toxicity indicate advantages comparable to other test agents.

90. *Estimation of Liver Size by Multiple Cut-Off Scanning Techniques.* **RAUF YAGAN, W. J. MACINTYRE, W. B. CHAMBERLIN, and J. H. CHRISTIE (Radioisotope Laboratory, Highland View Hospital, Cleveland)**

On the basis of approximately fifty liver weights and volumes obtained at autopsy, an empirical formula has been devised for the prediction of *in vivo* liver size. Variations in thickness of the liver have been accounted for by obtaining area scans at various counting rate cut-off levels. Reconstruction of a solid figure has been accomplished by projection of the three areas at distances proportional to the cut-off levels and calculation of two additional areas for a four segmented solid.

While most of the scans were made with cut-off settings of 20%, 60% and 75%, the formula is in general applicable for any settings as long as sufficient differentials are established between the successive levels. In our first series, preliminary results show no deviation greater than 20% with weight correlation. Corrections of density variation for volume-weight relationships are to be applied.

91. *Implant Dosimetry.* **C. G. AMATO, S. J. MALSKY, B. ROSWIT, and V. P. BOND (Medical Department, Brookhaven National Laboratory, Upton, Long Island, New York)**

A successful development program designed to produce a solid state clinical dosimeter is drawing to a close. The result is a practical miniature dosimeter. When properly shielded by a perforated gold shield, a low atomic number composition glass needle shows an accuracy of $\pm$ 7% in the energy range 45 kv to 1.33 mev. Dosimeter shield design, calibration procedure, fluorimeter-read design and operation, as well as implant techniques, are discussed. Clinical applications using radiation from teletherapy and brachy-therapy sources are presented.

A proposed technique under development to use the needles to determine the gamma exposure delivered by the gamma component of a neutron-gamma radiation environment are described.

The degree to which various types of phantoms duplicate body response to radiation is being investigated. Almost 1,000 shielded needles have been implanted in dead dogs and four types of phantoms. Preliminary results are given.

92. *Medical Reactor Technology.* **C. G. AMATO, S. J. MALSKY, B. ROSWIT, and V. P. BOND (AMF Atomics and Medical Department, Brookhaven National Laboratory, Upton, Long Island, New York)**

The direct and indirect application of neutrons to medicine is well known. Since a nuclear reactor is a copious source of neutrons, it must be given serious consideration for use as a medical instrument. Four reactors now exist or are being built which are intended for full or part time medical use.

A nuclear reactor may be operated as a steady state device or as a pulsed instrument. Two pulsed reactors and a low power steady state pool reactor designed by AMF Atomics are described. Emphasis will be upon concept, safety, location, utilization, staffing, medical economics and support facilities.

The reactors described are SYFTOR, a low-cost pulsed medical reactor designed to achieve maximum thermal flux for isotope production, and activation analysis; and the pool reactor. SYFTOR is a special purpose fast-pulsed reactor designed on the "time-of-flight" principle to achieve a high thermalized neutron pulse(s) with minimum accompanying resonance and fast neutrons. Gamma discrimination is high. The estimated gamma exposure per 10^{13} NVT is 100 rad. Both types of pulsed reactors have advantages derived not only from the basic concept, but also from application. The two operating modes are intercompared.

93. *Medical Reactor Neutron Spectroscopy.* **C. G. Amato (Medical Department, Brookhaven National Laboratory and AMF Atomics, Upton, Long Island, New York)**

Neutron energy can be resolved in the range from thermal energy to 12 mev using a sequence of radioactivants. Each radioactivant has a threshold for a nuclear reaction below which no reaction effectively occurs. Activation is due to all neutrons having energies above this threshold. When a series of such foils are activated, the neutron number flux is computed for each and then by subtracting the flux values for two detectors, the flux is obtained for neutrons lying within the energy region defined by the thresholds of the two detectors.

The cadmium difference technique, resonance activation integral and determination of an effective fast cross section are discussed and illustrated. Effects of foil thickness are stressed.

The method requires only the ability to measure radioactivity and to convert count rate to disintegration rate. It is a methodology within the reach of any medical unit engaged in neutron investigations.

Results obtained by applying this technique to the BMRR and IRL are given. Emphasis is upon the determination of thermal neutron penetration in a simulated brain as a function of heavy water moderator thickness.

94. *Determination of Liver Function With I^{131} Rose Bengal.* **George J. Carroll (Suffolk, Virginia)**

The use of I^{131} Rose Bengal as a test for liver function has been in use since 1955. In this laboratory an evaluation has been made using the head clearance, liver pick-up, and abdominal excretion with the use of a single probe. A series of patients have been studied in collaboration with various other liver function tests in determining the practical application in a general hospital without the use of expensive equipment. Its use in this hospital has proved of extreme value. The use of one of these tests; the head clearance is a simple and practical measure of abnormal liver function. Cases are presented to demonstrate the above points.

95. *Alterations in Thyroid Function Associated with Cancer.* **Sidney Rubenfeld, D. Joseph Pastorelle, and Carl J. Collica (Bellevue Hospital, New York)**

INFORMATION FOR AUTHORS

The Journal of Nuclear Medicine will publish original articles in clinical medicine, basic and clinical medical research, physics and chemistry dealing with the use of isotopes in humans, and articles on related subjects. The latter includes dosimetry, instrumentation, protection, techniques and biologic effects contributing to the use or effects of isotopes in clinical medicine or the clinical effects of ionizing radiation. Articles are accepted for publication on the condition that they are contributed exclusively to this journal.

MANUSCRIPTS must be typed doubled or triple spaced, the latter being preferable, and with at least a one-inch margin on each side of a standard size page. The original with one carbon copy must be provided.

TABLES must have captions and be numbered consecutively in Arabic numbers.

ILLUSTRATIONS should be in black ink on hard white paper with all lettering of sufficient size and clarity to permit reduction. Each illustration must be identified by a label pasted to the back indicating its number, the author's name and an abbreviated title of the article. The top of the illustration must be clearly indicated. Illustrations must have descriptive legends grouped on a separate sheet (double spaced).

REFERENCES must be cited in the text by number in parentheses in order of appearance. A consecutive list according to reference numbers must be submitted on a separate page, double spaced. Literature references must be cited in the following order: name of author, title of article, name of periodical, with volume, page, month (day of month, if weekly) and year. Book references must be cited in the following order: author's name, name of book, editor's name (if any), city of publication, name of publisher and year of publication.

Unused manuscripts will be returned by regular mail. Used manuscripts are not returned, however, used illustrations are returned after the article is published.

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North Chicago, Illinois

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Long Island City, New York

Baird-Atomic, Inc.
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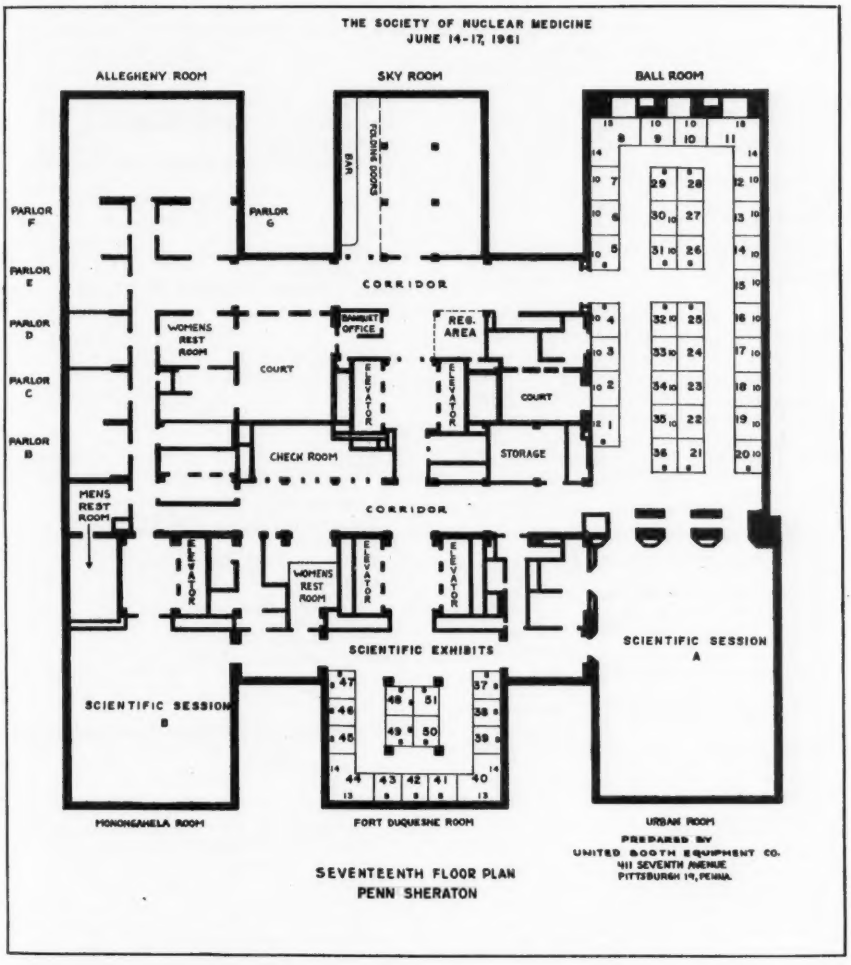

Plan of the seventeenth floor of the Penn-Sheraton Hotel in Pittsburgh, where the 8th Annual Meeting of the Society will be held, including both scientific and technical exhibits.

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8th Annual Meeting

SOCIAL HOUR AND BANQUET

Thursday evening, June 15, 1961

6:45- 7:45 Social Hour—Cocktails (cash bar)
8:00- 9:30 Annual Banquet—Dress, Optional
9:30-12:00 Dancing
9:30-12:00 Smoker and Shop Talk.

LADIES' ACTIVITIES*

Thursday, June 15, 1961

10:00 AM-10:15 AM	**Welcome and Introduction—Millard N. Croll, M.D.**
10:15 AM-11:00 AM	**General Approach to the Field of Radioisotopes—Joseph Greenberg, M.D.**
11:00 AM-11:15 AM	**Coffee Break**
11:15 AM-12:00	**Physical Principles—George W. Hinman, Ph.D.**
3:30 PM- 4:30 PM	**Guided Tour of Technical and Scientific Exhibits.**

Friday, June 16, 1961

10:00 AM-11:00 AM	**Clinical Application of Radioisotopes—Millard N. Croll, M.D.**
11:00 AM-11:15 AM	**Coffee Break**
11:15 AM-12:00	**The Commercial Production of Isotopes and Demonstration of Equipment—Paul Numerof, D.Sc.**

A special scientific program has been prepared for the wives of the Society's members. This program has been designed to present the many interesting aspects of nuclear medicine in a non-technical and layman's language.

Program Committee

RICHARD E. PETERSON, *Iowa City*
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SOUTHWESTERN
Herb C. Allen, Jr., *Houston*

AT-LARGE
Donalee Tabern, *Highland Park, Illinois*

The Society of Nuclear Medicine
Eighth Annual Meeting

General Arrangements Committee
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Annual Banquet and Recreational

Harry Bisel
General Duties

David L. Chamovitz
Recreational

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Recreational

Edward J. Pavsek
Exhibits

Paul Ritter
General Duties

Niel Wald
Public Relations and Press

President's Annual Report

We have become a large and influential Society. We must realize our responsibility and conduct the affairs and policies for the common good. In addition to our original aim of exchanging information about techniques and uses of radioisotopes, we are now confronted with requests for advice and cooperation from other Societies; and the need for training and standards in the field has become evident. Therefore, we should be pleased that we can now be of help to others but we must remember that our chief reason for being a society is to promote scientific and investigational progress. Individual professional gains must be secondary, and local problems should be settled in light of national policy. We should make certain that our national policy is developed with the progress of the local chapters in mind. It is very heartening in this respect that during the year, chapters have had regular meetings with excellent scientific programs. It is hoped, even though we have members all over the world, that each one can be actively associated with a regional chapter.

During the past year the Journal of the Society finished its "shakedown cruise" and is now "At Sea Under Full Steam". Our finances are in good shape but we must be prepared to expect additional expenses such as more pages for the Journal and perhaps more frequent publication in the coming years.

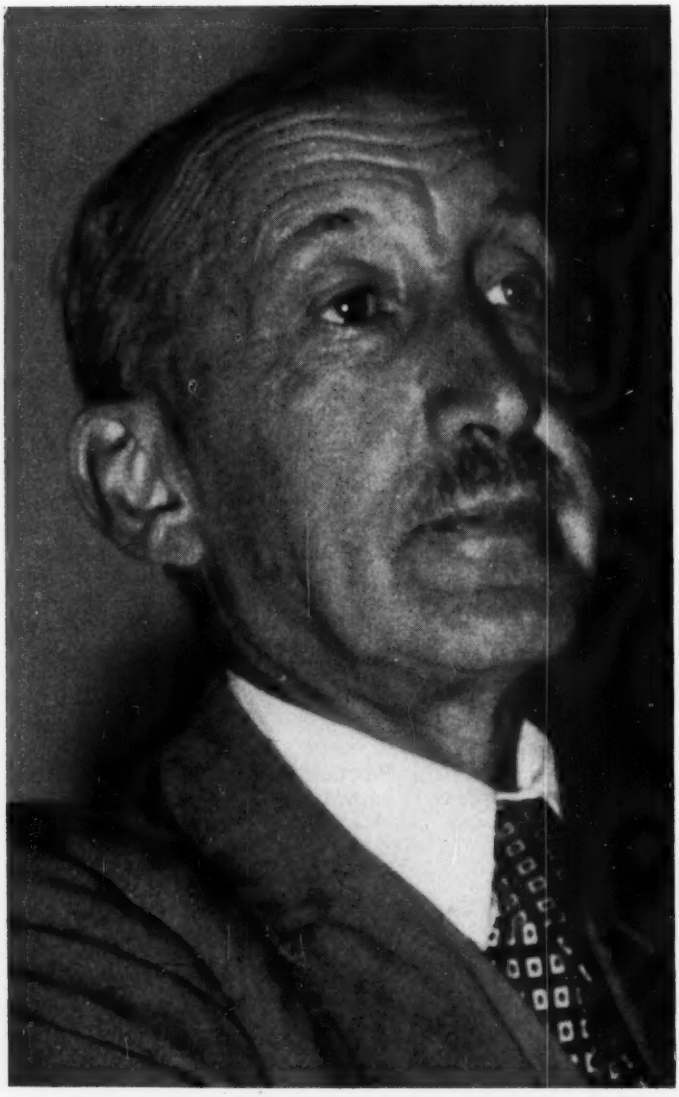
The meetings of the Executive Committee have been extremely well attended and all chapters have been represented. The spirit and efficiency with which the committees worked on the affairs of the Society is worthy of deep appreciation by all members of the Society. Dr. J. R. Maxfield has presented the report of his Committee in the form of a Jurisdictional Map of Chapters. This was accepted in general and detailed modifications will be worked out as they are needed. Dr. Kaplan has presented a report on Standard Nomenclature for Radioisotope Procedures. The entire committee on Education has been very active and our appreciation to them is hereby noted. All other Committees, both formal and ad hoc, have been functioning and there will be other reports of interest at the June meeting.

Dr. Richard Peterson and his Program Committee are to be congratulated on their most successful efforts to provide the Eighth Annual Meeting with a complete and stimulating program. I have been aware, through almost weekly conferences with Dr. Peterson, of the time and intensive efforts on the part of the Program Committee.

In addition to the officers and other members of the Executive Committee, I wish to thank Dr. George Thoma for his tremendous effort in behalf of the Journal, and Mr. Sam Turiel for his efficient handling of the business affairs. It has been a pleasure to work with them and an honor to serve the Society. I will soon join the dedicated group of Past-Presidents who, though without power, will lend a sympathetic ear to any one with problems or ideas pertinent to the Society.

I wish to express my confidence in the new President, Dr. Lindon Seed, and to congratulate him and the Society as he takes over and to assure him of my and your continued support during the coming year.

Titus C. Evans
President



Professor George C. de Hevesy

Professor George C. de Hevesy, of the Institute for Organic Chemistry and Biochemistry, at the University of Stockholm, Sweden, is to be this year's Nuclear Pioneer Lecturer. Although he is known first of all for his numerous pioneering investigations and his eminence as a teacher, he very properly is a first-hand reporter and historian of some of the most momentous events in the history of science.

Professor de Hevesy was born in Budapest August 1, 1885. He earned the doctoral degree at the University of Freiburg in 1908. He then went to Zurich for postgraduate work in physical chemistry. He was one of twenty in the audience attending Einstein's inaugural lecture as Associate Professor of Theoretical Physics. In 1911, to prepare for investigations suggested by Haber, he went to Rutherford's Laboratory in Manchester to become familiar with techniques for studying the conductivity of electricity in gases. During the years 1911-1914, he was associated with the discovery of the atomic nucleus, the use of a forerunner of Geiger's Beta Counter for detecting alpha particles, the setting up of the first X-ray spectograph by Moseley, and the discovery of cosmic rays by Hess. He visited Madame Curie in her laboratory many times after he began work with Radium D in 1912.

Professor de Hevesy's most notable investigations started with his failure to separate Radium D (Pb^{210}) from large amounts of radioactive lead chloride, at Lord Rutherford's request. After over a year of exhaustive disheartening effort, he decided to try and make the best of the situation and reverse the problem. In 1913, along with F. A. Paneth, he added pure Radium D to a known amount of lead salt so as to follow the paths of lead atoms "by using Radium D . . . as an indicator." In 1923, he used the tracer principles for the first time in a biological problem: Thorium B (Pb^{212}) to study the absorption and translocation of lead nitrate in bean plants. He was the first to use stable isotopes in clinical isotope dilution studies when in 1934 he used deuterium oxide to measure body water and its turnover. Following the discovery of artificial radioactivity in 1935, he initiated the use of artificial radioisotopes (P^{32}) as tracers in biological problems. In 1936 he described the principles of neutron activation analysis and published the first results using this technique two years later. In 1942 he described the first *in vitro* radioisotopic labeling of erythrocytes with its clinical use for measuring blood volume. His investigations have also included the fields of geochemistry, biochemistry, medicine, and radiobiology. His work has continued undiminished with his output of scientific papers being numerous and significant.

Professor de Hevesy created the tracer concept, established the classical principles of its use, and made the pioneering application of the technique, first with natural radioisotopes, then stable isotopes, and finally, artificial radioisotopes. It seems entirely justified to equate the importance of the isotopic tracer technique with that of the microscope. He and others using isotopic tracer techniques have revolutionized concepts of the metabolism of living systems.

As would be expected, honors have come to him from throughout the world. He received the Nobel Prize in Chemistry in 1943 and the second Atoms for Peace Award in 1959. He has been awarded four honorary degrees.

Professor de Hevesy has been an honorary member of the Society of Nuclear Medicine since 1959. He has expressed his pleasure in joining with us on this occasion to honor the memory of Madame Curie and her contemporaries.

CALENDAR OF EVENTS

Date	*Name of Course or Meeting*	*Place*
June 3-11	Meeting on Radiotherapy with High Powers—in conjunction with the 4th International Medical-Surgical Film Festival	Turin, Italy
June 4-8	American Nuclear Society	Pittsburgh, Pennsylvania
June 13-16	Symposium on Whole Body Counting	Vienna, Austria
June 14-17	*Society of Nuclear Medicine*	*Pittsburgh, Pennsylvania*
June 22-24	The Endocrine Society	New York, New York
June 22-24	American Physical Society	Mexico City
June 26-30	American Medical Association Section on Radiology	New York City
July 16-22	4th International Conference on Bio-Medical Electronics	New York City
August 1-4	International Congress of Biophysics	Stockholm, Sweden
August 6-26	Summer Course in Nuclear Physics	Varenna, Italy
August 10-16	5th International Biochemist Congress including Section on Radiation Effects on Biochemical Processes	Moscow, USSR
August 23-31	Conference on Radioisotopes in the Biological Sciences	To be announced
August 28-31	European Society of Haematology	Vienna, Austria
September 3-10	7th Inter-American Congress of Radiology	Sao Paulo, Brazil
September 26-29	American Roentgen Ray Society	Miami Beach
October 17-19	4th Japan Conference on Radioisotopes	Tokyo, Japan
November 7-10	American Nuclear Society	Chicago, Illinois
December	Symposium on the Programming of Research Reactors	Vienna, Austria

This Calendar of Events will contain basic information on special courses and meetings of interest to members of The Society of Nuclear Medicine. If you desire more complete information, Mr. Samuel N. Turiel, Administrator of The Society will be pleased to supply you with the name and address of the convening body or sponsoring organization, upon receipt of your request.

JOURNAL OF NUCLEAR MEDICINE 2:169, 1961

Marie Curie and Her Contemporaries

THE BECQUEREL-CURIE MEMORIAL LECTURE[1]

George de Hevesey, Ph.D., Dc. Sci., M.D.[2]

Stockholm, Sweden

MARIA SKLODOWSKA'S YOUTH

Marie Curie was Polish born, her maiden name was Sklodowska. Her father was a high school teacher, an able physicist; her mother was a teacher as well. They were keen patriots and most unhappy about the sad fate of their fatherland. Poland was under the heel of tsarist Russia. Supervisors were sent from Moscow to verify if the school children were brought up as Russian patriots and were taught extreme loyalty towards the Tsar, his family, and the Russian Government. Father Sklodowska got into difficulties with the supervisors, difficulties which further contributed to Marie Sklodowska's hatred towards the tsarist regime. The hatred was so deeply rooted that Maria and her schoolmates cheered the news of the murder of the Tsar Nicolaus the Second.

She was a hard worker with a sharp brain, the best scholar of her class. Finishing highschool not yet 18 years old she became a governess in the house of a well-to-do family, trying to make some money that would enable her to study outside Poland. Both Germany and Austria were enemy countries occupying Polish territory. She chose France, a free country, where science and art had a high standing.

Maria Sklodowska left for Paris and intended to return to Warsaw after finishing her studies. The goal at which she aimed ardently was to work for her country. She first hesitated on what to study, the choice being between sociology, literature and science. She finally decided on the last mentioned discipline.

While governess for three years she earned little money. In those days the German railways had four classes. The fourth class was much like a freight car in which just a bench was placed. Maria Sklodowska could only afford a fourth class ticket when travelling through Germany. She arrived in Paris in the fall of 1891 with a minimum of luggage.

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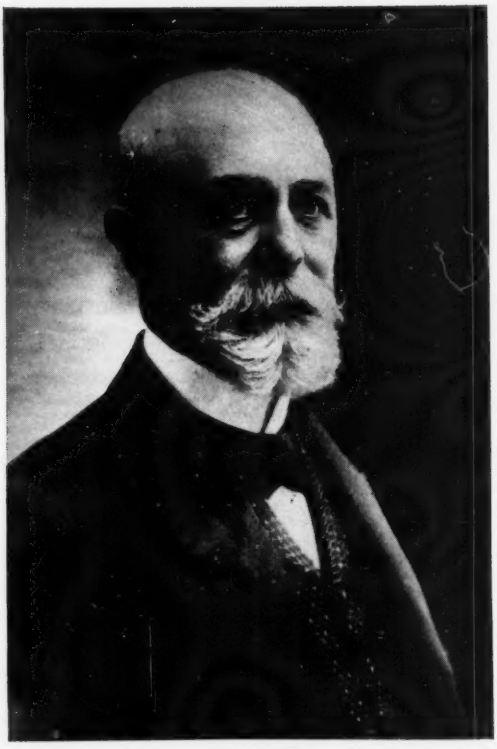
1. Second Annual Address in the Nuclear Pioneer Series: Presented at the Eighth Annual Meeting, The Society of Nuclear Medicine, Pittsburgh, June 15, 1961.

2. Research Institute of Organic Chemistry, University of Stockholm, Stockholm, Sweden.



Henri Becquerel

Pierre and Marie Curie in laboratory where Radium was discovered about 1904.

STUDENT IN PARIS AND MARRIAGE

Aided by her brother-in-law, an M.D., she could rent a room on the 6th floor, below the roof of an old large apartment house. She had 3 francs a day to live on and could only afford to buy two or three sacks of coal yearly which she had to carry up to her room herself. The room was cold and she was lonely, but, as she wrote home, she could concentrate undisturbed on her studies. What little money she had she mostly invested in books; hardly any was left for food. While attending a lecture at the Sorbonne she fainted. Her brother-in-law soon found out that she was suffering from a pronounced anaemia. He was interested in finding out what she ate and looked around in her room. The kitchen utensils were unused, she lived on cherries and chocolate. He took her to his apartment for a while to bring her in a better shape.

Maria Sklodowska who attended the first lecture at the Sorbonne on the 3rd November, 1891, soon found out that her French was poor and that the teaching of physics in the Polish schools lagged much behind what was taught to French children. But she worked hard and passed her examination with the best grade.

After obtaining her degree she was given a stipend by the Society For The Promotion Of the Interest Of The French Industry. She was to compare the magnetic properties of French steel samples handed her by the famous Professor Le Chatelier. Maria Sklodowska was to carry out the investigation in the physics department of the Sorbonne which was under the direction of Professor Lipmann, a very distinguished physicist who was the first to take coloured photographs and later obtained the Nobel prize for his work.

The room available in the physics laboratory was very restricted, furthermore Professor Lipmann wished her to help him. She had to analyse minerals, catalogue his collection of rock samples, and so on. This was an unhappy state of affairs and when she met a compatriot, the physicist Kowalski, professor in the University of Neuchatel, who visited Paris, she complained about her unsatisfactory placement in Lipmann's institute. Kowalski was on friendly terms with a young but already famous physicist, Pierre Curie, and promised Maria Sklodowska to contact her with him in the hope that he might place her in his laboratory.

Pierre Curie was born in Elsasse in 1854 as the son of a medical practitioner. I did not have the privilege of meeting him. He suffered, at only 47 years of age, an untimely death. Deep in his thought, pondering about his problems, he was knocked down by a heavy horse-driven lorry in the crowded streets of Paris. But I happened to know Marie Curie quite well. I never failed to call on her when passing through Paris. I was sure to find her in her laboratory surrounded by girl assistants carrying out experiments, crystallizing, precipitating. In the twenties, when calling on her I also met her daughter Irene and her assistant Joliot who later became her son-in-law. The subject of the doctoral thesis of the latter was the electrochemistry of polonium, a problem in which a decade earlier we were much interested with my late friend Paneth. Thus we had common interests.

I recall vividly a visit, when engaged in the concentration of actinium in a lanthanum sample obtained from pitchblende, Madame Curie presented me with a specimen of actinium concentrate. I always considered this specimen as one of my most precious belongings. Each time I look at the bottle containing the sample I find it deeper and deeper coloured indicating the long span of years which have passed since I met this remarkable personality and great pioneer.

Pierre Curie was much impressed by Maria Sklodowska. She was very intelligent, had a solid knowledge of physics, was straight forward, shared his radical views on politics, which she acquired in her youth and never changed. She was a beautiful girl as well. Pierre Curie wished to marry her, but she declined. She felt as a patriot it was her duty to return to Poland and to work for her country. They then discussed the possibility for Pierre Curie to follow her to Warsaw, but finally decided that they should marry in Paris. The wedding took place on the 26th of July, 1895.

They had 300 francs monthly to live on. Not much, but more than the monthly 90 francs Maria Sklodowska had at her disposal while a student. The purchasing power of money was in those days very much greater than today and the pretensions of the scientist very much smaller.

Shortly after being married the Curies were reading periodicals one evening. Marie Curie happened to glance at a paper published in the *Comptes Rendus*, the Proceedings of the Paris Academy of Sciences, in which Henry Becquerel announced the discovery of a radiation emitted by uranium. Before picturing the impression which the reading of this paper made on Marie Curie, I wish to be permitted to describe the happenings which preceded Becquerel's discovery.

HENRY BECQUEREL'S DISCOVERY

It was the progress made in producing high vacua which made it possible to carry out experiments of the type done by Crookes, Hittorf, J. J. Thomson, Lenard, and others. These experiments led to the discovery of the electron and the elucidation of its properties. It was his interest in this type of problems which induced Röentgen to study electric discharge through a vacuum tube. The phosphorescence of a screen covered with barium platinum cyanide which by chance happened to be placed in the vicinity of the vacuum tube led to the discovery of Roentgen rays.

The discovery made understandably an immense impression on his contemporaries, especially on the physicists, but on none a greater impression than on the eminent French scholar Henry Becquerel.

Becquerel was born in Paris, December 15, 1852. When 26 years old he was appointed to the Museum of the History of Natural Sciences as aid to his father, who was professor of physics in this institution. In 1892 he became successor to his father filling a chair already rendered illustrious by his father and grandfather, and earlier, by Gay-Lussac. The Becquerel family furnishes to students of heredity a most striking illustration of transmitted capacity. Their scientific

activity covers nearly the whole of the nineteenth century and part of the twentieth. The phenomenon of phosphorescence which fascinated Henry Becquerel was a field in which both his father and grandfather were much interested. The news of Röentgen's discovery, the phosphorescence shown by the walls of the discharge tube and of the barium platinum cyanide screen under the effect of the newly discovered rays deeply impressed Becquerel. The idea passed his mind that possibly all substances showing the phaenomenon of phosphorescence may emit Röentgen rays.

He soon found that sun-excited uranium acted on a photographic plate protected by black paper from the effect of light. His observation made him tremendously happy. He then devised another experiment in which, between the plate and the uranium salt, he interposed a sheet of black paper and a small cross of thin copper. On bringing the apparatus into daylight the sun had gone, so it was put back into the dark cupboard and left there for another opportunity of insolation. But the sun persistently kept behind clouds for several days. Tired of waiting, Becquerel developed the plate. To his astonishment instead of a blank, as expected, the plate had darkened under the uranium as strongly as if the uranium would have been previously exposed to sunlight, the image of the copper cross shining out white against the black background.

This was the beginning of a long series of experiments which led to the discovery of the Becquerel rays in the same year (1896) in which the Röentgen rays were discovered.

DISCOVERY OF POLONIUM AND RADIUM

The reading of the paper of Becquerel deeply impressed Marie Curie and induced her to remark to her husband that she doubted that uranium should be the only element emitting the new type of rays. She added that she intended to investigate all existing elements in the search of radiating ones. With the enthusiasm and energy which characterized her, she started the next morning to initiate her studies. She took one element after the other looking for the same type of radiation as is emitted by uranium. It did not take her long to discover that thorium emits Becquerel rays.

Marie Curie then concentrated her interest on minerals containing uranium. Pitchblende, one of the first minerals investigated by her, contains about 60 per cent of this element, and as already found by Becquerel that the intensity of radiation emitted by an uranium compound is proportional to its uranium content, she expected 1 gram of pitchblende to act on her measuring instrument with the same intensity as does 0.6 gram of uranium. She was much impressed to find the intensity of radiation emitted by 1 gram of pitchblende several times that of 1 gram of uranium. It was clear to her that pitchblende must contain an unknown element many times more radioactive per unit of weight than uranium.

The result of her investigation of the radioactivity of pitchblende and also of the copper uranium phosphate mineral chalcolite, was presented to the Paris Academy of Sciences by Professor Lipmann on the 12th of April 1898, by the

man in whose laboratory she felt so unhappy when faced with the task to compare the magnetic properties of steel samples; an unhappiness which resulted in her meeting Pierre Curie. The same year her study on the magnetic properties of steel samples was published as well.

The paper introduced by Marie Curie to the Paris Academy of Sciences in April 1898 in which she reported on the radioactivity of pitchblende and chalcolite was followed on the 18th of July by a joint paper of Pierre and Marie Curie announcing the discovery of polonium which they separated with bismuth from pitchblende. But the latter was, even after the removal of polonium, exhibiting a strong activity, thus must have contained another radioactive body.

Half a year later the Curies announced the discovery of the body looked for, which they precipitated with barium and called radium. Barium sulfate precipitates played a most important role in the history of radioactivity. When isolating radium this element was coprecipitated with barium; so was ThX in Rutherford and Soddy's experiments which lead to their theory of successive atomic transformations. Nuclear fission was detected by Otto Hahn by precipitating barium sulfate and demonstrating that the activity observed is due to barium.

The Curies did not doubt for a moment that they had discovered two new elements, polonium and radium. However, the French chemists were critical; they wished the elements to be isolated and their atomic weights determined before they were willing to acknowledge their discovery. Considering that 1 part of radium is found in about 5 million parts of pitchblende it was clear that an isolation of radium requires large amounts of pitchblende.

The only uranium mine in those days was that of Joachimsthal (now called Joachim) located in Bohemia, now Czechoslovakia. The mines were Austrian state property. Uranium had no great value in those days. It was mainly used in the glass industry. Uranium containing glass has a beautiful green colour. Large silver ore deposits made Joachimsthal famous. Coins minted from 1519 onwards in Central Europe and Scandinavia contained Joachimsthal silver. Being minted from Joachimsthal, silver the coins were called Thaler in Central Europe, Daler in Scandinavia and—Dollar in the United States of America. The word dollar originates thus from Joachimsthal.

The influential Austrian geologist Sues was instrumental in putting forward the request of the Curies for pitchblende to the Austrian Government which generously presented them with 10,000 kg of pitchblende.

The premises at the disposal of the Curies where they had to separate radium were very primitive, without heating and proper ventilation, but which did not prevent them from working with great enthusiasm. In 1902, only 45 months after the discovery of the new element, they succeeded in preparing 100 mg. of radium. While Pierre Curie was mainly interested in the study of the radiation emitted, Marie Curie did the chemical work.

While working on the isolation of radium they discovered the induced radio-

activity and interpreted this phaenomenon as due to radium emanation "infecting" the surroundings of radium salts. They noted among other things that radium incessantly produces heat and measured exactly the heat produced.

The Curies had a modest income only, their family being enlarged, they had to fill teaching posts to earn money. Marie had to teach physics at a high school for girls. This took much of her time and energy.

It was only in 1904 that they could leave their primitive premises and move into a better laboratory in Rue Cuvier belonging to the School of Physics and Chemistry of the City of Paris, where all their work was done. It was in 1909 that Madame Curie obtained an up-to-date laboratory erected at the suggestion of the director of the Pasteur Institute, Rous, simultaneously with the erection of an institute for Curie therapy in close vicinity of the former.

BIOLOGICAL EFFECTS OF RADIUM RAYS

Two years after the discovery of radium, Giesel, a manufacturer of chemicals in Braunschweig in Germany, succeeded in preparing small amounts of radium chloride and soon Wakhoff and he found that the rays emitted by radium have a destructive action on the epidermis. The reading of papers of Wakhoff and of Giesel published in 1900 induced Pierre Curie to place a radium sample for 10 hours on his arm and to study its effect on the skin. He was most enthusiastic about the appearance of an erythema which covered a surface of about 6 sq.cm of his skin. Later a wound became visible which healed after a lapse of 4 months but not without leaving a mark behind.

Henry Becquerel reacted in a very different way. He traveled to London where he had to address the Royal Society. There was a tube containing radium chloride in his waistcoat pocket and on arriving home in Paris he discovered a wound on his chest produced by the radiation emitted by the radium sample. He was very much upset and reproached the Curies to have discovered a substance which emitted a radiation having such an unpleasant effect.

A few years later trials were made to cure lupus erythematosis and cancer with the aid of radium rays. It was uterine cervical cancer which was first treated with Curie therapy in 1905. The treatment of this type of cancer remains the chief therapeutic application of radium rays. When writing a contribution on this topic, the present author followed the statistical data on irradiation of uterine cervical cancer up to 1955. Until that date 360,000 cases were recorded and their number today cannot be much less than 500,000.

The successful medical application of radium was a source of immense satisfaction to Madame Curie. When Pierre Curie was delivering his Nobel lecture in 1903 no therapeutic results were yet obtained with radium rays, but Pierre Curie emphasized the importance of the biological effects of radioactive radiation and remarked among others that in the hands of a criminal radium could become a very dangerous substance.

THE CURIES AND BECQUEREL OBTAIN THE NOBEL PRIZE

To have obtained the Nobel prize contributed enormously to the fame of the Curies and helped them to obtain more generous support of their investigations.

They obtained jointly half of a physics prize, the other half being allotted to Henry Becquerel. In 1911 Madame Curie obtained the chemistry prize alone, thus being the only person who ever obtained two Nobel prizes.

In 1935, 24 years later, her daughter Irene—who, as a young girl, witnessed the previous handing over of the Nobel prize to her mother by the King of Sweden—and her husband Frédéric Joliot obtained the prize for their fundamental discovery of artificial radioactivity. The Curie family was thus now in possession of five Nobel medals.

One year before becoming a Nobel laureate Pierre Curie, strongly pressed by his friends, applied for a seat in the Academy of Sciences of Paris. His application was dismissed however. The Curies' fame had not yet sufficed to become a member of the Paris Academy of Sciences. He was elected in 1905 while Marie Cuire failed to become a member. She was elected a member of the Academy of Medicine in 1922.

After the tragic death of Pierre Curie his wife continued her research alone; she further purified radium, determined its atomic weight and prepared metallic radium. She also had much trouble with the production of an international radium standard.

In the earlier phase of her activities, Madame Curie had restricted laboratory facilities and had to fight economic difficulties. With increasing fame both her laboratory facilities and her personal economy improved more and more. Andrew Carnegie realized the immense importance of her work and supported her laboratory from 1907 onward.

In 1920 on the initiative of Mrs. Meloney, the women of the United States collected 100,000 dollars to enable her to purchase 1 gram of radium. The gift was handed over to her in Washington by President Harding and she was most heartily welcomed and fêted by numerous institutions during her stay in the United States.

MARIE CURIE'S AILMENTS AND DEATH

Marie Curie had a powerful adversary, this was her poor health. She was plagued by cataracts, had difficulties with her kidneys, her lungs, she felt weak for long periods and succumbed to an aplastic anaemia in 1934 in the Hills of Savoy. How far the handling of strongly radioactive substances was responsible for her ailments and death is difficult to answer. Her mother suffered from tuberculosis which may explain her lung trouble. Already in 1910 when meeting Madame Curie at the Solvay Congress in Brussels, Rutherford wrote to his wife: ". . . Madame Curie was there. She looked very wan and tired and much older than her age. She works much too hard for her health. Altogether she was a

very pathetic figure." She carried out all that fabulous work in spite of being handicapped by poor health. Her life illustrates the mighty power inherent in the passion for scientific research. Mme. Curie (Rutherford wrote in his obituary note in Nature) retained her enthusiasm for science and scientific investigation throughout her life. Quiet, dignified and unassuming, she was held in high esteem and admiration by scientific men throughout the world.

BECQUEREL'S VIEW ON THE ORIGIN OF THE ENERGY OF RADIATION

Henry Becquerel was pondering on the source of the energy incessantly given off by uranium shortly after the discovery of the radiation emitted by that element. He considered several explanations arriving finally at the view put forward in an evening discourse at the Royal Institution in London on March 7, 1902, six years after making his fundamental discovery. "The origin of this energy," he said "is an enigma. On the material hypothesis it does not seem improbable to liken the phaenomenon to the emission of perfume by an odorous body; to compare the emanation to a kind of gas the particles of which are of the order of magnitude of those of the electrolytic ions; and to identify the radiation with cathode rays produced by the dislocation of these ions, giving at the same time an emission of X-rays. The dissipation of energy therefore can be associated with the disintegration of active matter." He then added: "However it explains most the facts, no accurate experiment exists which gives sanction to this hypothesis."

ATOMIC TRANSFORMATION

After the lapse of less than 10 years, in 1902 ingenious experiments were devised which proved unambiguously that we are faced in the phaenomenon of radioactivity with atomic transformation, not with a single one but a series of successive transformations, that while an almost infinitesimal fraction of uranium is transformed daily some of the transformation products of uranium, such as radium A, disappears almost quantitatively in the course of minutes. The radiations emitted represent energy released in the course of the transformation process. These results, some of the most important ones achieved in the course of the history of the natural sciences, are due to Rutherford and Soddy.

ERNEST RUTHERFORD

Rutherford was the seventh son of a farmer of very modest means living at Nelson, New Zealand. In 1935, when I delivered the Scot lectures in the University of Cambridge, I had the unique privilege to stay with Rutherford. One evening he was in high spirits and told me the history of his first experiment. When he was a little boy he was sent to fetch the cow of the family and a trunk of wood as well. He got the ingenious idea to fix the trunk to the tail of the cow, which he found to be a great help. Reaching home he noticed, however, that the trunk was gone and so was the tail of the cow—happenings which had the most unpleasant consequences for him.

Rutherford had more success with his later experiments. In the Canterbury

College of the New Zealand University he began research on the magnetic properties of iron, exposed to high frequency oscillations. He succeeded in his trials to produce electric waves in those pre-marconian days and to pick these up at a distance of a few kilometers. This very promising work was interrupted when he was awarded, in 1895, an 1851 Exhibition Science Scholarship to study under J. J. Thomson in Cambridge.

The Cavendish Laboratory where he was to work was the most famous physical laboratory in those days being engaged mainly with the study of the properties of the electron and the conduction of electricity in gases. J. J. Thomson, the director, had a remarkable instinct for knowing which were the problems most worth working on and the general nature of methods of investigation most likely to succeed.

Rutherford carried out very successful researches in these fields. When starting his work at the Cavendish Laboratory he tried to find out whether the ions produced by uranium behaved in the same manner as those produced by X-rays and ultra-violet light. He found it to be so. He quickly noticed that there were two types of rays present which he called, from the first letters of the Greek alphabet, alpha and beta rays. The α rays were cut off, or absorbed, by a stout sheet of paper, but the β rays were a hundred times as penetrating. He published his work when he was later at McGill in Montreal.

The penetrating γ rays were discovered by Villard in Paris in 1900.

In a paper published by Rutherford jointly with J. J. Thomson in 1896 the important hypothesis was put forward that the conductivity of electricity through gases produced by irradiation with Röentgen rays is due to the formation of positively and negatively charged particles.

In the Cavendish and also in the Manchester Institute the laboratory steward an able, versatile, experienced man, highly interested in the work going on and in the research workers, played quite an important role in the running of the laboratory. This was the case even in some other laboratories in those days. I worked for a short time with the great German chemist Haber who was the first to produce ammonia from nitrogen of the atmosphere by availing himself of a catalytic process, which was a very great advance. The name of Haber's laboratory steward very appropriately was Kirchenbauer (church builder). When discussing experiments to be carried out, Haber usually introduced the discussion with the words "If God and Kirchenbauer so wish we shall carry out the following experiment . . ."

To be appreciated by the laboratory steward spoke much in favour of a young physicist. J. J. Thomson's eminent laboratory steward who served later under Rutherford as well, had a great admiration for the young Rutherford and recalled, approvingly, decades after Rutherford left the Cavendish, that none of the young physicists working in this laboratory could swear as forcefully at his apparatus as did the young Rutherford.

Mainly due to the successful work carried out in the Cavendish Laboratory, Rutherford was offered, in 1908 when only 27 years old, the chair of physics in the McGill University of Montreal.

THE ALPHA RAYS

In 1902 Rutherford succeeded in deflecting α rays emitted by radium both by a magnetic and an electric field arriving at the conclusion that the mass of the α-particle was about twice that of the hydrogen atom. The proof that the α-particles consisted of charged atoms of matter projected with an enormous velocity at once threw a flood of light on radioactive processes, in particular on investigations of fundamental importance carried out simultaneously by him in collaboration with Frederic Soddy.

SUCCESSIVE ATOMIC TRANSFORMATION

In contrast to radium, thorium compounds were easily available and this fact induced Rutherford and Soddy to study the radioactivity of thorium. They dissolved thorium nitrate in water, added a small amount of barium nitrate and precipitated the barium as sulphate. Testing the radioactivity of the lattter they found it strongly active while the activity of the thorium nitrate simultaneously decreased. The daily measurement of the activity of both fractions brought out that the barium precipitate lost its activity with time while the thorium fraction recovered its original activity hand in hand with the first mentioned losses. This was, in those days, a startling observation.

Rutherford mentioned, when recalling these early days, that they moved the barium precipitate into a neighbouring room to see if the phaenomenon they observed depended on the presence of thorium in the vicinity of the barium sulphate.

It did not, however, take them long to find an explanation of their remarkable observation. Thorium is transformed into another element at an exceedingly slow rate. We are, however, not faced with a single transformation process but with a series of transformations. ThX, into which thorium is transformed, is converted by disintegration into a new element as well, not at a slow rate as is thorium, but rapidly. After the lapse of a few weeks ThX is almost fully transformed, whilè the thorium nitrate sample recovers its original ThX content.

THORIUM EMANATION

When passing an air stream through the ThX sample the air was found by them to be radioactive, a very short living body, thorium emanation, being formed. To prove that they discovered a gaseous element Rutherford and Soddy wished to condense it by cooling the air stream with liquid air. No liquid air was available in Montreal. They had to fetch a liquid air plant from Europe. The plant arrived and the whole personnel of the physics institute went to the harbour to fetch it in the early hours of the morning. In the late hours of the night the plant was fitted up, liquid air produced and demonstrated that the

strongly radioactive air stream entering a U-shaped tube is not active any more when leaving the liquid air cooled tube—an example of Rutherford's mighty pushing power. At the same time most of his work was carried out without visible effort in a most remarkable way.

Today we read about the sequence of thorium series, of uranium series, and it all looks so simple. To establish these series required an immense ingenuity and a tremendous work carried out almost exclusively by Rutherford and his school. Beside elucidation of the series of transformation, the properties of different types of radiation were among other topics studied with great energy in Rutherford's laboratory.

Always intensely occupied with the progress of his own work, Rutherford had the patience to listen to every young man when he felt he had any reasonable idea on his mind.

COUNTING OF α-PARTICLES

The tool which Rutherford appreciated more than any other was the α-particle and it was the study of the behaviour of α-rays which led him to his greatest success.

In 1902, as already mentioned, he succeeded in deflecting α-particles from their path with the aid of a magnetic and also of an electric field, and he could conclude that the mass of the α-particle was about twice that of the hydrogen molecule. About the same time, when putting forward their theory of successive disintegration with Soddy they remarked: "The results obtained so far point to the conclusion that the beginning of the succession of chemical changes taking place in radioactive bodies is due to the emission of the α-rays, i.e. the projection of a heavy charge from the atom".

From the numerous investigations of Rutherford in which α-particles were involved one of the most outstanding ones was the counting of the scintillations and thus the number of α-particles falling on a screen of phosphorescent zinc sulfide. The number of the scintillations per second on a screen agreed with the number of α-particles impinging on it counted by the electrical method.

The electrical counting method of α-particles was worked out by Rutherford and Geiger. The latter was Rutherford's assistant for eight years. Later, when filling the chair of physics in the University of Kiel he constructed the Geiger-Müller tube for counting of β-particles. Geiger, a very able experimental physicist and congenial man, could not forsee what an immensely important role his tube would have in the development of atomic sciences and atomic industry.

THE NUCLEUS OF THE ATOM

The counting of scintillations produced on a zinc sulphide screen with the aid of a microscope was a device of extreme simplicity. It was when applying this device that Rutherford discovered the existence of the atomic nucleus, a discovery which I had the very great privilege to witness from close quarters.

A minute fraction of the α-particles was deflected strongly from their path which was interpreted by Rutherford to be due to the presence of a positively charged nucleus in the centre of the atom which strongly deflects only α-particles passing nearby. From the deflection figures he calculated the nucleus to have a radius of 10^{-15} cm. which compares with the radius of the atom making out 10^{-8} cm.

Already in those days Rutherford anticipated the presence in nuclei of a heavy neutral constituent of a mass closely coinciding with that of protons. I heard him repeatedly discuss the probable existence of such particles and the difficulties one would encounter when trying to locate them. The neutron was discovered in his laboratory two decades later by Chadwick who was his assistant in the Manchester days.

NIELS BOHR

In the spring of 1912 on a Sunday afternoon which I spent in Rutherford's hospital house I asked him from where the β-particles emitted by the atoms originate. Do they come from the nucleus or from the outer part of the atom? Rutherford answered: "ask Bohr," and Niels Bohr who was present explained that the β-particles connected with an atomic transformation, the β-particles emitted, for example, when atoms of radium B are transformed into atoms of radium C originate from the nucleus and these only. The name nucleus was suggested by Bohr. The latter saw with a fabulous foresight the whole development which the science of the atom would take in the years to come. It was, at that date, clear to him that while the explanation of the radioactive disintegration had to be sought in the constitution of the nucleus, the ordinary physical and chemical characteristics of the elements manifested properties of the surrounding electron configurations. He saw also that we have to base the physical and chemical properties of an element on the nuclear charge; on the atomic number, as it was called later, which is a multiple of the elementary unit of electricity. He remarked that, "Argon is the wrong argon", because, and this Bohr realized at a time when the notion of isotopes had not yet emerged, the heavy argon-40 is represented to an abnormal extent in the isotopic mixture making out argon. We know today that the disintegration of K^{40} leads to the formation of Ar^{40} adding an ever-increasing amount of this heavy argon isotope to its isotopic mixture.

Bohr had also foreseen in 1913 the possible existence of tritium and stated his view in a discussion following the talk of J. J. Thomson at the Birmingham meeting of the British Association of Advancement of Science in which also Marie Curie, Raleigh, Oliver Lodge, Ramsey, Larmor and Lorentz participated.

Rutherford did not appreciate in his Manchester days, some of the prestations of theoretical physicists but he had the greatest admiration for the scientific genius and unique personality of Niels Bohr. Through all the years he took much interest in his work including that in the philosophical implication of quantum theory.

Rutherford had the greatest admiration for the accomplishments and personality of Marie Curie but in spite of this he was not always anxious to share

her company. This is not necessarily a contradiction. Madame Curie loved to talk shop and to discuss details of chemical operations which she was carrying out. Rutherford occasionally discussed his own problems as well, but he liked to talk about politics, discuss problems of economics, talk about his friends and so on. He had no interest in chemistry and no great appreciation of chemists. He was highly amused about obtaining the Nobel prize for chemistry in spite, as he told us, of his utter lack of knowledge in the field of chemistry. When proposing the toast of the Chemical Engineering Congress of the World Power Conference in 1936, Rutherford remarked: "I cannot claim to be a chemist, but, on the other hand, I have often raided the borders of the chemist like a moss-trooper and returned with some loot",—an extreme understatement.

The above remarks further explain why in spite of his admiration of Marie Curie he did not always eagerly seek her company. At the Solvay Congress in Brussels in 1922 where both participated, we young people were instructed to look after Madame Curie which I did with the greatest enthusiasm. Her quiet dignity and power had to impress one and I considered it a unique privilege to be permitted to talk with her on problems of the chemistry of rare earth elements in which in connection with the separation of actinium she was much interested and which interested me as well in those days.

Possibly none of the great personalities about whom I have had the privilege to talk to you was more honoured, and collected more glory than Marie Curie in the later phase of her career. But none experienced so much hardship as she did in the earlier phase of her life and even in the course of her early scientific career. She experienced bodily and mentally cruel times. When these times were gone she lost her beloved husband and most closest collaborator when only 47 years old. In spite of all the glory experienced in the later part of her life, the above mentioned happenings left behind a trace of bitterness in her soul. This bitterness speaks from her biography of Pierre Curie in which she writes, "Our society in which a keen desire prevails for luxury and riches does not grasp the value of science. She does not understand that the science is a part of her most valuable heritage. She does not realize that science is the fundament of all progress, which facilitates human life and reduces suffering. Neither the authorities nor private charity provide science and the scientist with the support and means which are a necessity which is unavoidable if a successful work has to be carried out."

Times have changed radically to the better since these words were written. In achieving this change the marvellous accomplishments of Marie Curie and her great contemporaries, which influenced all branches of science and many of medicine, had a great share.

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On Being Well Named: A Standard Nomenclature of Radioisotope Procedures[1]

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DEFINITION

The use of radioisotopes as radioactive labels in medical and paramedical procedures has in recent years become widespread. A variety of labeled elements and compounds are employed in diagnostic, therapeutic and investigative procedures. The scope of application of these labeled substances has cut across the conventional compartments of specialization, and has become involved not only in the various fields of medicine but also in the physical ramifications of chemistry, physics and engineering as applied to medicine. As a consequence of the heterogeneous applications in this field, information is scattered in a large variety of literature. It is written by, published for, and read by a polyglot group of many disciplines.

Excellent justification exists for allowing the uses of radioactive materials to develop unhindered in these many areas without attempting to correlate or systematize the information as it relates specifically to the radioisotope aspect of the problem. However, a reasonable approach to classifying this burgeoning knowledge, particularly in the biological sciences, would be the development of a comprehensive system of nomenclature. A standardized nomenclature would clarify the literature which is currently replete with procedures named after jargon from a dozen different fields, monumental tributes in the form of proper names of contemporary workers, and euphonic commercial terms.

A special problem exists in relation to by-product material licensing. The proper identification of a procedure could be accomplished with relative ease with adequate nomenclature. The ambiguity that exists may easily lead to faulty identification of a procedure. For example, the term RAI, which is often used as a synonym for 24-hour I^{131} uptake by the thyroid, has no precise meaning and may be construed to identify any procedure using I^{131}. To lend meaning to licensing procedures, a precise identification of terms is needed.

1. From the Radioisotope Service, Veterans Administration Hospital, Hines, Illinois.

A similar precision is needed in recording procedures in hospital charts. Inadequate identification may make it impossible to know the details of radioisotope administration to a patient. Such pertinent information may be excluded as the isotope used, the amount of activity, the route of administration or the physical or chemical form. The medico-legal significance of proper chart keeping is obvious.

The widespread coverage of health insurance plans are involved in the need for nomenclature. The setting of fee schedules and the positive identification of procedures are needed to make the communication between the doctor or hospital and the insurance company adequate.

Assuming the necessity of a Standard Nomenclature of Radioistope Procedures (SNORP), a scheme is necessary that conveys the maximum information and yet is brief and accurate. Such a consideration immediately rules out jargon, proper names, and commercial trade names. The use of a physiologic terminology would represent a substantial improvement. However, limiting the information to physiologic information only would not adequately communicate the pertinent facts. Accepting the need for physiologic criteria as an important aspect of terminology, an approriate generic classification scheme may be developed.

A generic scheme has been derived for diagnostic or therapeutic procedures, in which those aspects of the procedure involved which will give a clear and comprehensive description are identified.
The details of such a generic scheme are outlined below.

SCHEME FOR DIAGNOSTIC NOMENCLATURE

A—Isotope
1. Compound
2. Physical state

B—Organism
1. Organ
2. Tissue
3. Cell, etc.

C—Function Measured
1. General
2. Specific

D—Method
1. Detector
2. Assay material
3. Assay technique

E—Author

Examples of Diagnostic Nomenclature

Se^{75} selenomethionine pancreatic localization by scintillation detector (Blau)
I^{131} Hippuric Acid Cerebral Hemisphere Differential Circulation Volume *(Oldendorf)*

SCHEME FOR THERAPEUTIC NOMENCLATURE

A. Route of Administration

B. Isotope

1. Compound
2. Physical state

C. Therapy

D. Disease or Pathologic State

E. Method

F. Author

Examples of Therapeutic Nomenclature

1. Interstitial Iridium^{192} metallic pellet therapy for pelvic tumor by implant *(Liegner)*
2. Intracavitary Yttrium^{90} chelate therapy of malignant effusions by injection *(Greenberg)*

DISCUSSION

The above classification scheme is of such a general nature that attempts to classify new and unusual applications of radioisotopes have uniformly resulted in applying a generic name which clearly explained the procedure undertaken.

The scheme is adaptable to coding systems which may readily be recorded or correlated by punch card or computer systems.

The availability of standard nomenclature information is as important as the proper classification scheme. The information should be published and widely disseminated so that it will be available in libraries and to hospitals, research organizations, insurance companies, interested individuals and to various agencies which may regulate or control the use of isotopes.

Publication of nomenclature information should be undertaken at frequent intervals so that a minimum lag exists between the publication of a new procedure and its inclusion in a Registry of Standard Nomenclature. This would best be accomplished in a periodical publication dealing with isotope procedures. It is suggested that this information be included in *The Journal of Nuclear Medicine* as a part of the regular issue and that at less frequent intervals a complete compilation of the nomenclature be published, possibly as a supplement to the regular issues. The registry could be further useful as a bibliograhic source of the procedures listed.

The staffing needs of such a registry should be explored, and could probably operate with a medical librarian and clerical help. Professional consultation should not present a major problem. The support of such a registry is of sufficient importance to those in the field to warrant aid from a granting agency. The problem of support is being explored at this time. It would appear advantageous for authors of new procedures to file titles of reprint material with such a registry as it would insure the inclusion of their procedure in a widely available reference source.

The information published by a registry of nomenclature should supplement rather than duplicate the information periodically published by the AEC on distribution and utilization of isotopes and related publications.

SUMMARY

In summary, the need for a standard nomenclature of radioisotope procedures is stressed. The value of the nomenclature to interested persons and institutions is discussed. The existence of a registry to compile, publish and disseminate the nomenclature appears desirable.

We emphatically believe that any nomenclature to be useful must be simple, informative and available.

Announcement to Authors
Preliminary Notes

Commencing with the October, 1961 issue, space will be reserved in each issue of THE JOURNAL OF NUCLEAR MEDICINE for the publication of one preliminary note concerning new original work that is an important contribution in Nuclear Medicine.

Selection of the preliminary note shall be on a competitive basis for each issue. One will be selected after careful screening and review by the Editors. Those not selected will be returned immediately to the authors without criticism. Authors may resubmit a rejected or revised preliminary note for consideration for publication in a later issue. The subject material of all rejected manuscripts will be considered confidential.

The text of the manuscript should not exceed 1200 words. Either two illustrations, two tables, or one illustration and one table will be permitted. An additional 400 words of text may be substituted if no tables or illustrations are required. Only the minimum number of references should be cited.

Manuscripts should be mailed to the Editor, Dr. George E. Thoma, St. Louis University Hospital, 1325 South Grand Blvd., St. Louis 4, Missouri. They must be received before the first day of the month preceding the publication month of the next issue, e.g., preliminary notes to be considered for the January issue must be in the hands of the Editor before December 1.

JOURNAL OF NUCLEAR MEDICINE 2:187, 1961

Intragastric Beta Irradiation With Ru-Rh^{106} In Human Subjects: Results With Single Doses.[1,2]

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INTRODUCTION

Beginning in 1909 (1) x-ray therapy for peptic ulcer has been the subject of much interest. In 1935 Kruglikowa et al. (2) remarked that they knew of over 200 papers on this topic. The early results were not impressive on critical analysis. Enthusiastic remarks on results in 800 cases were made by Hedfeld (3) in 1948, but his data were lost during the war. The painstaking work of Palmer, Kirsner and their associates was summarized in 1957 (4) on 20 years of experience with 723 cases. Their data established clearly that x-ray therapy given according to modern principles was a useful adjunct to the medical management of duodenal ulcer and would significantly reduce the recurrence rate. Deleterious side effects were extremely rare but use of this therapy by others has been limited. Recently there have been promising results with supervoltage x-ray in patients with gastrojejunal ulcer (5) and with gamma rays of cobalt^{60} (6). The possible advantages of delivering radiation to the gastric mucosa from within the stomach were recognized by McGeorge (7) who employed radium needles with some success but the method was not used widely.

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2. This work was supported by a grant from the U. S. Atomic Energy Commission. Read before the Seventh Annual Meeting, Society of Nuclear Medicine, Estes Park, Colo., June 25, 1960.

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The application of an intragastric technique with a beta emitting source would appear to obviate many of the objections to radiation therapy, if adequate and measured dosage could be delivered uniformly to the gastric mucosa. The limited tissue penetration of the beta particles would limit the amount of radiation delivered to other organs. This approach has been studied in gastric fistula dogs by a number of investigators using P^{32} (8-10) I^{131} (11), A^{41} and Kr^{87} (12). We have previously reported results with Sr^{90} and Ru-Rh^{106} (13). All of the work on dogs indicated that gastric acidity could be substantially reduced, apparently without important side effects. No publications have appeared in which any of these techniques have been described as suitable for use in human subjects.

The reasons for our selection of Ru-Rh^{106}, its decay scheme and the details of fabrication and use of the device are given in our previous papers on experiments with dogs (13, 14). A brass cylinder 6 mm in diameter and 18 mm. long was electroplated with 100 millicuries of Ru-Rh^{106} and covered with a very thin plating of silver. The cylinder was affixed to a slide wire and encased in a steel shield attached to a thin flexible shaft (Fig. 1A). The slide wire could be manipulated from the operating end of the instrument (Fig. 1B) to expose the

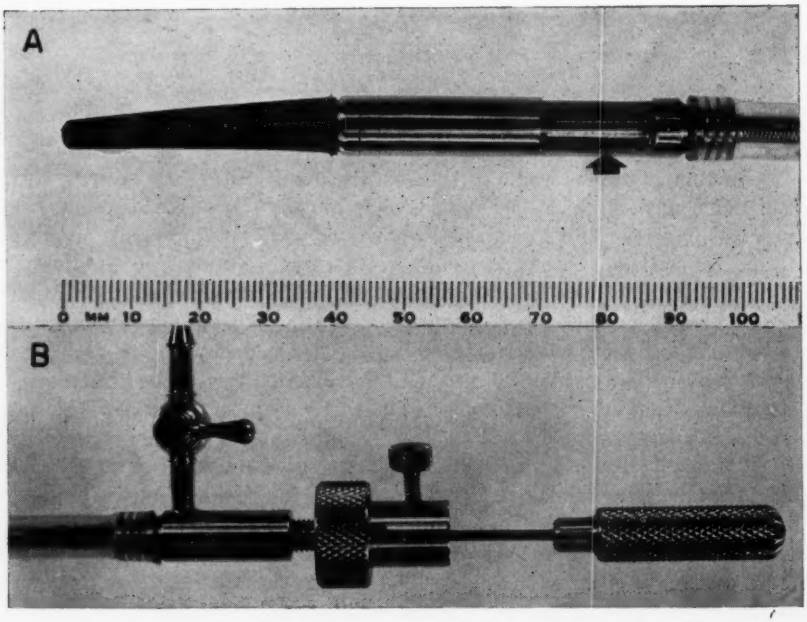


Fig. 1A—1B. (A) Tip of instrument. Arrow points to isotope cylinder in exposure position. (B) Operating end.

isotope. A rubber balloon enclosed the irradiating unit, inflatable from the operating end of the instrument. Estimation of dosage rate, radiation pattern and absorption curves were determined with an especially designed extrapolation chamber (15).

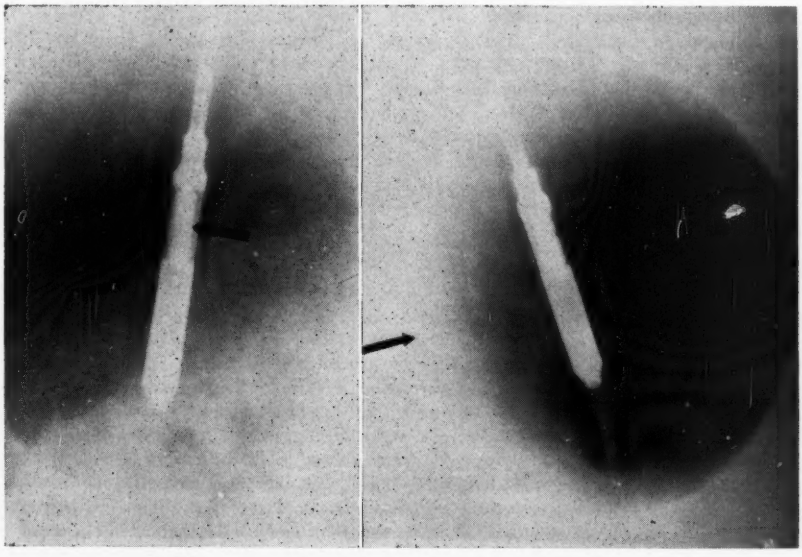
It was our intent to learn first the effects of single doses on gastric acid secretion and on morphology of the gastric mucosa.

MATERIALS AND METHODS

Six patients were treated. The first three had malignant disease not involving the stomach, but had abdominal complaints. The last three had prolonged and severe symptoms attributed to peptic ulcer, and had been considered for gastrectomy.

The instrument was passed by mouth using pre-medication as for gastroscopy. The balloon was inflated with 525 cc. of air giving a sphere with a radius of approximately 5 cm. Fluoroscopy confirmed that the isotope cylinder was approximately in the center, and the isotope was then exposed. The unit could be retained for periods of several hours without difficulty. During treatment several spot films were routinely made as a record. Occasional momentary fluoroscopic checks were made to ascertain that the balloon had remained fully inflated and that the isotope had remained approximately centered (Figs. 2A, 2B). On conclusion of the exposure the isotope was retracted into its shield. The air was then aspirated from the balloon and its volume measured to determine whether leakage had occurred. The instrument was then promptly withdrawn.

All patients were observed and gastric analyses performed at frequent intervals up to 22 months following treatment. Basal secretion was collected for one hour, and then for an additional 90 minutes following histamine (0.01 mg



2A 2B

(A) Spot film showing usual position of irradiation unit in the air-inflated intragastric balloon. Arrow points to exposed isotope cylinder. (B) Case 4, showing eccentric position of isotope cylinder.

base/kg body weight) or 50 mg. Histalog injected subcutaneously. The methods of aspiration and titration were the standard ones (16). Basal secretion was studied to detect minor suppressive effects of treatment, and histamine, later Histalog, to judge possible reduction of parietal cell mass.

Frequent gastroscopic examinations were made, usually with the Benedict instrument, so that simultaneous biopsies could be made from a known site. Routine blood and differential counts and urinalyses were performed several times weekly in the first few weeks after treatment and then at less frequent intervals. No changes from pre-treatment results were observed.

CASE PROTOCOLS

Case No. 1. E. S. was a 58 year old man with chronic lymphocytic leukemia since 1955. He was first seen by us in August, 1957 with complaints of epigastric discomfort and bloating. Physical examination was entirely normal. Barium studies of the upper and lower gastrointestinal tract, gall bladder x-rays, and gastroscopy were normal.

On 8/23/58 the patient received 200 rep at a rate of 8.4 rep/min for 24 minutes. The patient tolerated the procedure well and experienced no immediate or delayed ill effects. As shown in Figs. 3 and 4, no significant depression of secretory response occurred. Seven gastroscopic examinations showed minor changes culminating in superficial gastritis at the sixth week, which had subsided by the 12th week. On 12/17/58 the patient received a second course of radiation; 268 rep were given at 6.7 rep/min for 40 minutes. The procedure was again well tolerated and no adverse effects were observed. Gastroscopic examination again revealed superficial gastritis at the sixth week. He was observed for an additional period of seven months during which he was clinically unchanged.

Case No. 2. T. C. was a 55 year old male with chronic lymphocytic leukemia since 1954. He was first seen by us in October, 1957, with nonspecific gastrointestinal complaints. Examination revealed generalized lymphadenopathy and hepatosplenomegaly. His white blood count was 154,000 with 100 per cent lymphocytes. Upper gastrointestinal series was negative. Gastroscopy showed the gastric mucosa to be pale and slightly atrophic, but otherwise normal.

On 10-15-57 the patient received 300 rep at 7.9 rep/min for 38 minutes. He tolerated the procedure well and suffered no gastrointestinal complaints referable to it except minimal pharyngeal discomfort for one day. Gastric analyses were performed one and two weeks following radiation. He expired suddenly 15 days after irradiation. Post mortem findings were those of chronic lymphocytic leukemia and a large ancient gastric ulcer scar. Numerous fine petechiae scattered in the gastric mucosa were the only findings attributable to irradiation.

Comment: Doses of 200, 268 and 300 rep in the first 2 cases did not cause any significant decrease in output of acid after histamine or Histalog. Basal acid output was also not decreased.

Case No. 3. A.S. is a 57 year old female, who in 1956 had x-ray and radium treatment for a Class II invasive carcinoma of the cervix. She was first seen by us in December, 1957, with a two-year history of burning right sub-costal and epigastric pain, relieved by alkalis, and episodes of melena. Examination revealed undernutrition, slight distention of the abdomen, and hepatosplenomegaly. Upper G. I. series was negative, barium enema showed diverticula, and sigmoidoscopy showed a narrowing of the rectosigmoid secondary to radiation therapy. There was no evidence of recurrent or metastatic carcinoma. The patient was unable to tolerate gastroscopy.

On 1/14/58 the patient received 450 rep (6.4 rep/min), for 75 minutes. During the procedure there was air loss from the intragastric balloon of 190 cc owing to a faulty stopcock. The procedure was well tolerated, and the patient complained only of minor pharyngeal irritation for the following day. Serial gastric analyses were performed until June, 1958.

It is strikingly shown in Fig. 3 that basal secretion of acid disappeared after the treatment, and did not return for the 20 week period of observation afterward. Fig. 4 shows that a transitory decrease in stimulated acid output may have occurred.

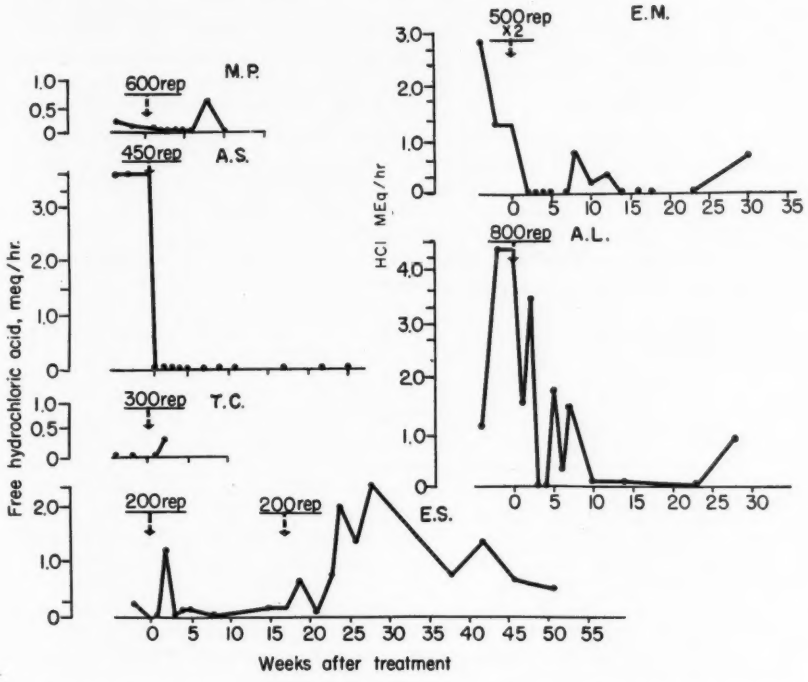


Fig. 3. Basal output of free hydrochloric acid in 1 hour in the weeks following irradiation.

Case No. 4. M.P., age 58 was first seen in February, 1958, when she entered the hospital with gastrointestinal bleeding. She had had a similar episode in 1954, and the diagnosis of duodenal ulcer was made. She had been maintained on ulcer management for a time following her first hemorrhage, but for the past three years had taken only small doses of antacid for symptoms. Physical examination was not remarkable. Upper G.I. series revealed a markedly deformed antrum, pylorus, and duodenal bulb, with no clearly demonstrable ulcer crater. Gastroscopy on 2/22/58, revealed chronic atrophic gastritis.

On 2/25/58 the patient received 600 rep at 5.9 rep/min for 102 minutes. During the treatment a leak developed three times requiring additional air. With the leaks the isotope source assumed a position closer to the lesser curvature of the stomach as shown in Fig. 2B. The patient experienced only minor pharyngeal discomfort following the procedure.

Eight weeks after irradiation the patient began to complain of abdominal pain and nausea during gastric analyses. These symptoms became worse after the tenth to the twelfth weeks, and she was hospitalized at the end of the 13th week with coffee-ground emesis and symptoms of pyloric obstruction. Upper G. I. series revealed two large gastric ulcers on the lesser curvature. (Fig. 5A). These were also seen at gastroscopy, which also showed diffuse acute gastritis involving the entire mucosal surface, but minimal in the pre-pyloric portion. Despite continuous intensive management severe pain persisted. On 6/12/58, 15 weeks after irradiation, the patient underwent a sub-total gastric resection. A photograph of the ulcers is shown in Fig. 7.

Comment: A transient fall in acid output after Histalog, reaching approximately 30 percent of control levels, occurred 2 weeks after treatment. Thereafter slow irregular recovery was observed.

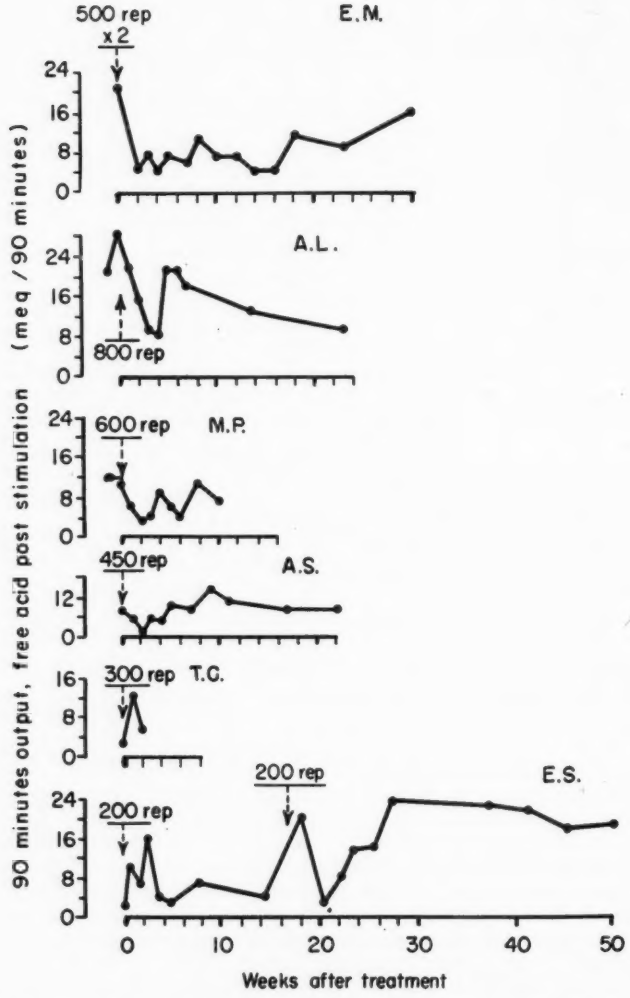


Fig. 4. Total output of free hydrochloric acid for 90 minute period following histamine (0.01 mg./kg. body weight) or Histalog (50 mg.) in the weeks following irradiation.

Case No. 5. A.L. The patient is a 48 year old male with a history of severe constant ulcer symptoms since 1955, with temporary and intermittent relief under rigid out-patient management. He obtained complete relief when hospitalized on several occasions. On 4/4/58 he received 800 rep at 5.35 rep/min for 150 min. The procedure was well tolerated, with only minimal pharyngeal discomfort. Gastric analyses (Fig. 3) revealed basal achlorhydria from the 10th to the 23rd week after treatment, showing a rise at the 28th week. There was a sharp drop in free acid output after Histalog during the first four weeks after treatment, after which a sharp rise occurred with a gradual drop over the next 18 weeks to approximately 50 percent of pretreatment levels (Fig. 4).

Gastroscopic examination 2½ weeks after irradiation revealed a slightly edematous somewhat friable mucosa but otherwise normal in appearance. In the eighth week following irradiation the patient began to have severe abdominal pain, and barium meal revealed a large gastric ulcer on the lesser curvature. (Fig. 6). He was hospitalized for 7 weeks on rigid ulcer management, and serial x-rays revealed slow healing, although the patient remained asymptomatic. Gastroscopic examination revealed a benign ulcer on the lesser curvature, surrounded by an area of acute gastritis. After discharge from the hospital on ulcer management he had recurrent minor pains typical of ulcer. Since the ulcer showed no further healing, on 11/28/58 a partial gastrectomy was performed. The surgical specimen is shown in Fig. 7. Except for inability to regain weight, the patient had done well when last seen 15 months afterward, 22 months after irradiation.

Case No. 6. E.M., a 53 year old female, had a history of upper abdominal discomfort since 1951. In September, 1957, she was hospitalized for massive upper gastrointestinal hemorrhage. On 5/22/58 and 5/23/58 the patient received 500 rep at 5 rep/min for 100 minutes on each day, a total of 1000 rep. Except for mild pharyngeal discomfort, her immediate post-treatment course was uneventful. Serial gastric analyses (Figs. 3, 4) and gastroscopies were performed. Her one hour basal output of free acid was zero two weeks after radiation, and except for a rise during the eighth to twelfth weeks after treatment, there was basal achlorhydria until the 30th week. The output of free acid following stimulation showed a prompt drop and 18 weeks after treatment there was a slow rise. Gastroscopy at 3 weeks after radiation showed marked superficial gastritis with tiny superficial ulcerations. Fifteen weeks after treatment, gastroscopy showed normal mucosa.

Eight weeks after irradiation the patient began complaining of transitory ulcer-type symptoms. Upper G.I. series 8 months after therapy revealed a 1 cm gastric ulcer high on the lesser curvature. Despite intensive medical management for 6 months there was no healing, and on 8-27-59 partial gastrectomy was performed. When last seen in February, 1960, she was doing well and was without symptoms 21 months after radiation and 6 months after surgery.

RESULTS AND DISCUSSION

Gastric Acidity. In cases 3, 5 and 6 an apparently long-lasting decrease in basal acid secretion occurred. In case 4 the basal level was unusually low in control periods; the brief decline to zero level may represent a transitory effect. Thus it appears that this phase of secretion is decreased with single doses of 450 rep or over. Basal secretion is relatively easy to reduce with various agents, so this result is interpreted by us only as an index that some physiologic change occurred, parallel with obvious histologic changes.

In the patients given 450 rep or more, several or many periods of basal achlorhydria occurred (Fig. 3). As shown in Fig. 4, however, histamine or Histalog stimulation at those times usually evoked an abundant output of acid. Since stimulated acid output was only questionably and temporarily reduced it is clear that no long-lasting appreciable effect on parietal cell mass was obtained.

Gastroscopic observations were made in cases 1, 4, 5 and 6. In case 1 with seven examinations, minor generalized superficial gastritis was observed from the sixth to twelfth weeks, after which the mucosa appeared normal. Similar observations were recorded with his second treatment. In the three cases receiving large doses the gastritis was much more severe and the onset was as early as the third week (case 6), with apparent complete recovery at 15 weeks. When gastric ulcers occurred, however, the surrounding areas showed persistent inflammatory change.

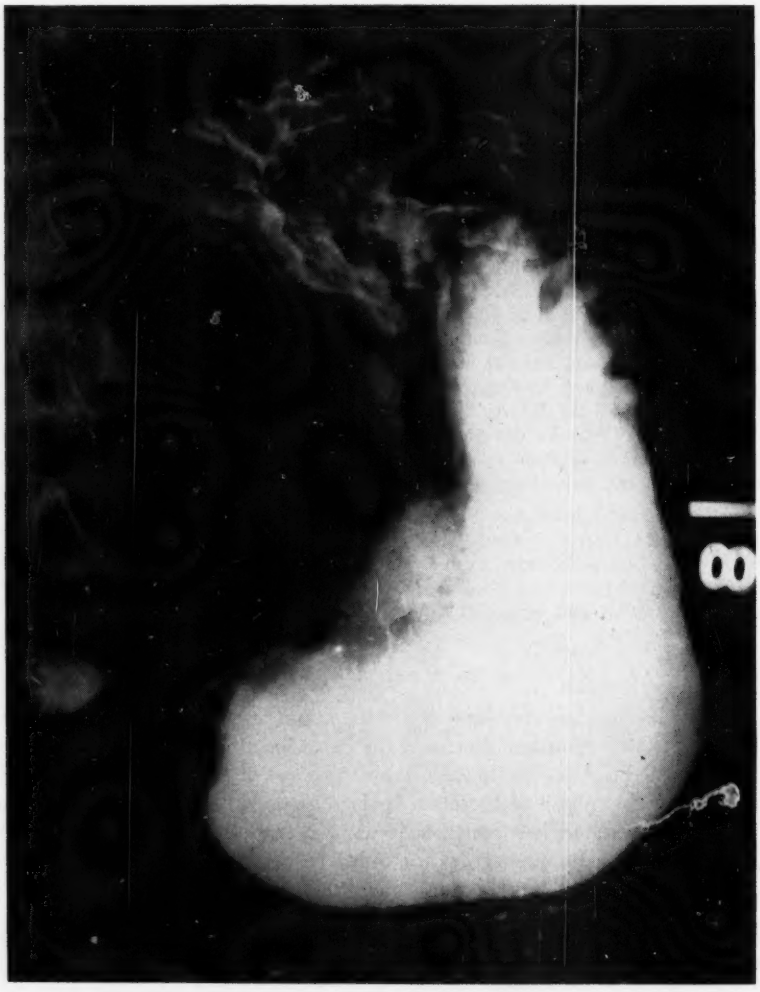


Fig. 5. Case No. 4, 600 rep. X-ray showing 2 large lesser curvature ulcers 13 weeks following irradiation. The surgical specimen is shown in Fig. 7.

Histologic changes were evident a week after therapy. In case 1 at that time the normal architecture was preserved, but there was degeneration of surface epithelial cells, neck glands, parietal and chief cells. Smooth muscle in the lamina propria and in the media of submucosal vessels also showed degenerative changes. There was no cellular infiltrate. At two weeks the histologic appearance was the same.

At one month there was disruption of glands and architecture with heavy infiltration of polymorphonuclear and eosinophilic leukocytes. There was focal regeneration of surface epithelium and neck glands with downward proliferation of neck glands. At seven weeks these changes were still present, but with less cellular infiltrate. Specimens after the second treatment consisted only of superficial epithelium, showing degenerative changes at two and seven weeks.

In the surgical specimens of the stomach in cases 4 and 5 it was possible to obtain 16 evenly spaced specimens of each. This provided opportunity to study the distribution of anatomic changes, at 3½ months after therapy in case 4 and at 7 months in case 5. The patterns of gross architectural alterations are shown in Fig. 7. In both specimens it is clear that the most severe changes persist along the lesser curvature, and intensely and more uniformly toward the pyloric portion. It was only in the distal part that severe grades of disruption were seen on the greater curvature.

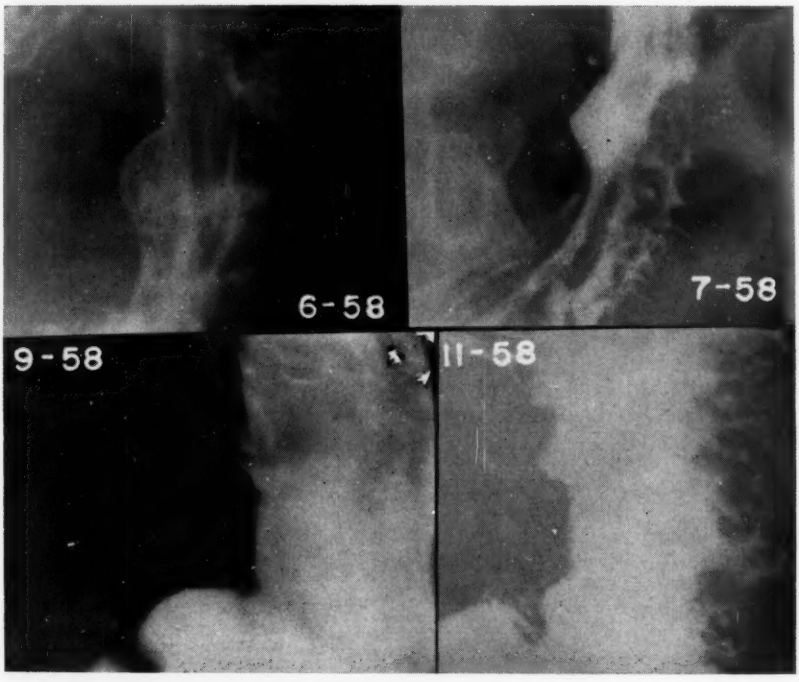


Fig. 6. Case No. 5, 800 rep. Serial views of gastric ulcer, showing slow healing. The surgical specimen is shown in Fig. 7.

The possible reasons for this distribution are interesting. Inflation of the balloon stretches the greater curvature more than the lesser curvature. This results in a tendency of the isotope unit to remain closer to the lesser curvature. This can usually but not always be corrected for by positioning the patient under fluoroscopic control. Presence of the spinal column also tends to keep the lesser curvature more fixed and aggravate this effect. Our observation indicates that isotope position is not the sole factor, because the distribution of alterations is the same in both specimens, and only in case 3 was the isotope cylinder observed to remain much closer to the lesser curvature. Further, even if dosage were uniformly distributed, the spine in close proximity to the posterior wall at the lesser curvature would serve as a source of back-scatter and increase the tissue dose in this region. Under these experimental circumstances, according to our absorption curves (15) about 70 per cent of the surface dose would be expected to penetrate the gastric wall and contribute to back-scatter.

The extensive persistent microscopic architectural changes in the prepyloric portion of the stomach in both specimens as shown in Fig. 7 is remarkable in view of the relatively low dosage in this region. This is due to its axial location in relation to the radiation source; our measurements indicate nearly zero dosage in the end-on position, owing to umbra effect (15).

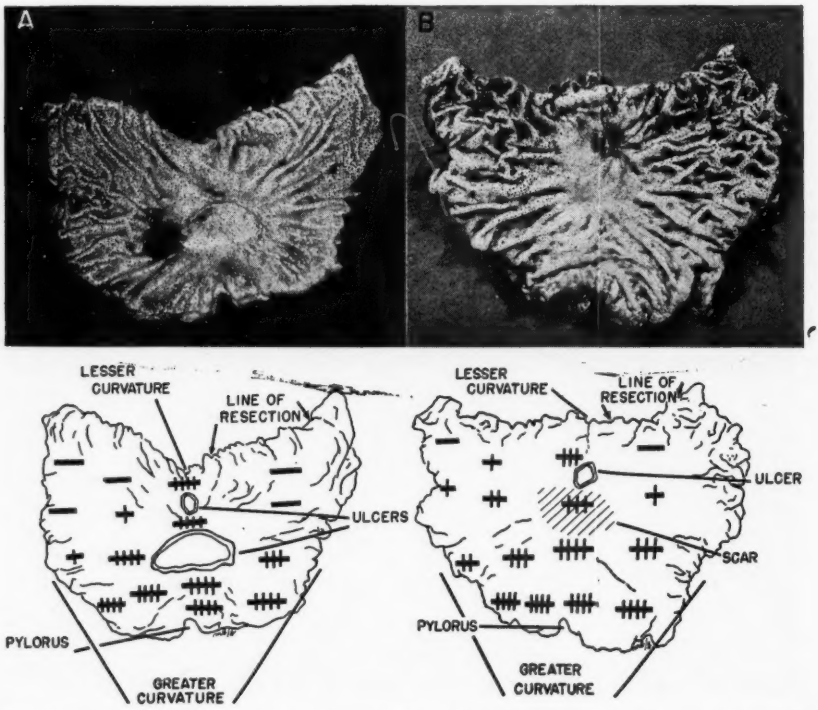


Fig. 7. Resected stomachs, cases 4 and 5, with diagrams showing distribution of residual microscopic architectural alterations. (a). Case 4, 3½ months after 600 rep.; (b). case 5, 7 months after 800 rep. Severe atrophy with disruption of glands is represented as 4+; similar but lesser changes, 3+; moderate, 2+; focal minor changes +.

These findings imply that the pyloric gland mucosa may be more "radiosensitive" than the fundic gland mucosa to have sustained severe injury with low dosage, and, since the specimens were obtained 3½ and 7 months after irradiation, less regenerative ability is also implied.

We have observed that many pyloric glands were present in those areas showing severe persistent changes, which is of interest in relation to the striking predilection shown by Oi (18) and his associates for gastric ulcer to occur in the border zone between pyloric and fundic gland areas.

Our observations on histologic changes, based on the limited amount of material we have obtained thus far, suggests two differences from the changes observed in patients treated with x-ray. As expected, we found the earliest changes in superficial epithelium and neck glands rather than in the deeper part of the glands as reported by Goldgraber et al. (17). At the peak of the histologic reaction our material showed far more polymorphonuclear leukocytes, with an influx of eosinophils later.

Observations on irradiation ulcer. In cases 4, 5 and 6, receiving 600, 800 and 1000 rep, slowly healing gastric ulcers developed. In the first two cases symptoms clearly referable to these lesions began eight weeks after therapy. In the third case the diagnosis was not established until eight months after treatment, but transitory mild symptoms were present after two months. The ulcers were all on the lesser curvature of the pars media, slightly toward the posterior wall. As described above in the discussion on histologic alterations, the most severe changes took place in that area. It was pointed out that this area receives maximal dosage of radiation owing to some degree of eccentricity of the isotope source. It is our hypothesis that an important additional factor is proximity of this region to the spine, leading to back-scatter. Possibly important support for this idea was provided by Ellinger (19) who reviewed the lierature on irradiation ulcer in man and animals and found that they "are always located on the lesser curvature or its vicinity, (so-called 'Magenstrasse')", regardless of the technique of radiation. It should be noted that this region is the site for most spontaneous gastric ulcers; the possible relation to pyloric gland transition zone has been mentioned above.

Histologically the ulcers are indistinguishable from chronic gastric ulcers of the usual benign type seen in surgical pathologic material. Clinically they are characterized by slow and incomplete healing with prolonged intensive therapy. In our experience and that of others such ulcers in dogs may remain unhealed for several years.

From our work with Ru-Rh^{106} and Sr^{90} in dogs and the observations in this paper and by others, it appears that chronic ulcers occur when a threshold dose is exceeded. This dose is 600 rep at the gastric mucosal surface under our experimental conditions.

SUMMARY AND CONCLUSIONS

1. Six patients have been given single treatments with beta radiation of Ru-Rh^{106} from an intragastric "point" source centered in a balloon inflated with 525 cc of air. Dosage estimated with an especially designed extrapolation chamber

ranged from 200 to 1000 rep at the surface of the mucosa. The dosage rate varied from 8.4 to 5 rep/min.

2. With doses of 450 rep and larger, in all but one instance there was abolition or substantial decrease in basal acid secretion. Histamine or Histalog-stimulated acid output was only questionably and briefly reduced, indicating that there was no real reduction in parietal cell mass.

3. Gross and microscopic anatomic changes were observed even with the smallest doses, 200 rep. These alterations became evident more quickly and were more severe as dosage increased.

4. With doses 600 rep and larger, chronic ulcers of the lesser curvature were observed.

5. Our technique of intragastric irradiation is technically feasible and safe, but the single dose method is not satisfactory for reduction of acidity. We are now employing fractionated dosage in the treatment of selected patients with peptic ulcer and patients with gastric neoplasm.

ACKNOWLEDGEMENTS

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Effect of Boiling and of Cyanide Ion on Serum Binding of Co^{60} Vitamin B_{12}[1,2,3]

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INTRODUCTION

Microbiologic techniques for estimating total serum content of vitamin B_{12} depend on an initial period of heating to free the vitamin from the protein-bound state in which most or all of it exists. This may be done, according to various investigators, by heating to 100° C for 15 to 240 minutes (2, 5, 7), to 90° C for 30 minutes (1), or to 120° C for six minutes (8). More complete recovery of the vitamin may occur if cyanide ion in low concentration is added to the serum before heating (8). Such assay methods are applicable to native serum and to serum to which vitamin B_{12} has been added for the purpose of estimating its unbound binding capacity. By bioassay, "free" vitamin B_{12} is that which supports the assay organism before heating the serum; "bound" vitamin B_{12} is that which becomes available after heating. We have attempted to complement the above information by studying the effect of boiling heat on the Co^{60} vitamin B_{12} binding capacity of normal human serum.

METHODS

Serum was obtained from blood bank donors and used immediately after clotting and separation or stored at −20° C until used. To one ml aliquots of serum in Visking cellulose sacs were added 1, 2.5, or 5 mμg Co^{60} vitamin B_{12}. Following two-hour room temperature incubation, these were placed in boiling water for 15-240 minutes, or first dialyzed in cold running tap water for 48 hours, then boiled as above. After boiling, all specimens were dialyzed in tap water for 48 hours. Sacs were then placed in four ml vials filled with concentrated sulfuric acid. After sac dissolution, contents were mixed and radioactivity counted in a well-type scintillation counter. Activity represented undialyzed or physi-

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2. Study supported by institutional grant, Nat. Cancer Inst., NIH, USPHS.

3. Co^{60} vitamin B_{12} was supplied by Merck and Co., Rahway, N. J.

cally bound vitamin B_{12}. Correction was made for vitamin bound on cellulose casing by dialyzing saline solutions of various concentrations of vitamin B_{12} 48 hours, then estimating residual activity. Boiling Visking casing had no effect on its dialyzing characteristics. To evaluate the isolated effect of cyanide ion on serum binding capacity for vitamin B_{12}, aliquots of serum with added vitamin prepared as above were dialyzed 48 hours in a Model B Oxford Multiple Dialyzer against an ammonium buffer, pH 8.8, or against buffer containing .0024 M NaCN. Bath solutions were changed every 12 hours.

RESULTS

Six sera were divided and, after incubation with vitamin B_{12}, dialyzed, then boiled 15, 30, 60, 120, or 240 minutes before redialysis. Figure 1 shows vitamin B_{12} to be freed partly after boiling 15 minutes, and freed in increasing amounts with longer heating until at four hours virtually no bound vitamin remains.

Twelve other sera were divided, boiled at once after incubation, and dialyzed. Results have been averaged and are shown in Figure 2. Again, degree of freeing of vitamin is proportional to duration of boiling. However, after 15 and 30 minutes of boiling in the presence of excess and presumably previously unbound vitamin B_{12}, there is binding of more vitamin than after simple dialysis.

When sera to which Co^{60} vitamin B_{12} in amounts up to 100 mμg/ml had been added were dialyzed against a dilute cyanide solution, the amount of vitamin B_{12} bound after 48 hours was no different than when dialysis was conducted against buffer alone. No study involving boiling in presence of added NaCN was performed.

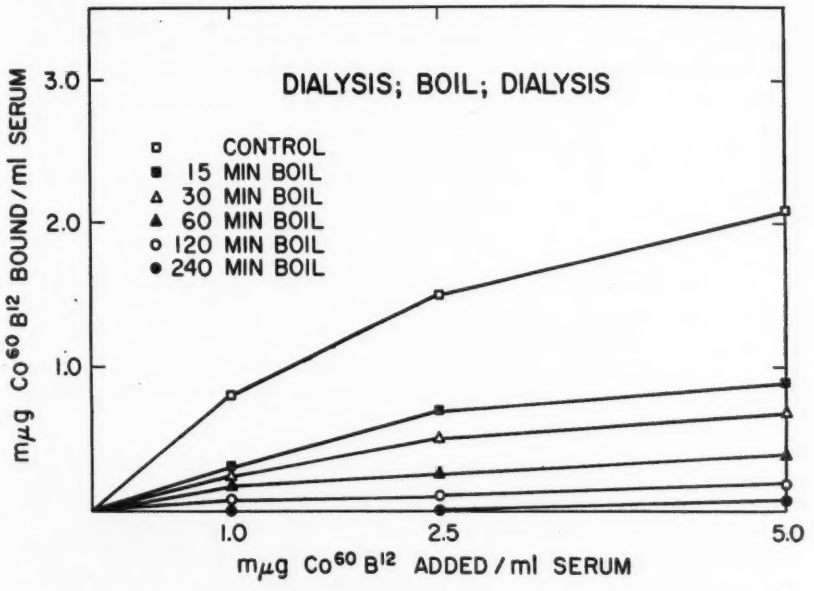

Fig. 1. Effect of heat on serum binding of added Co^{60} vit B_{12}. Excess vitamin has been removed by prior dialysis.

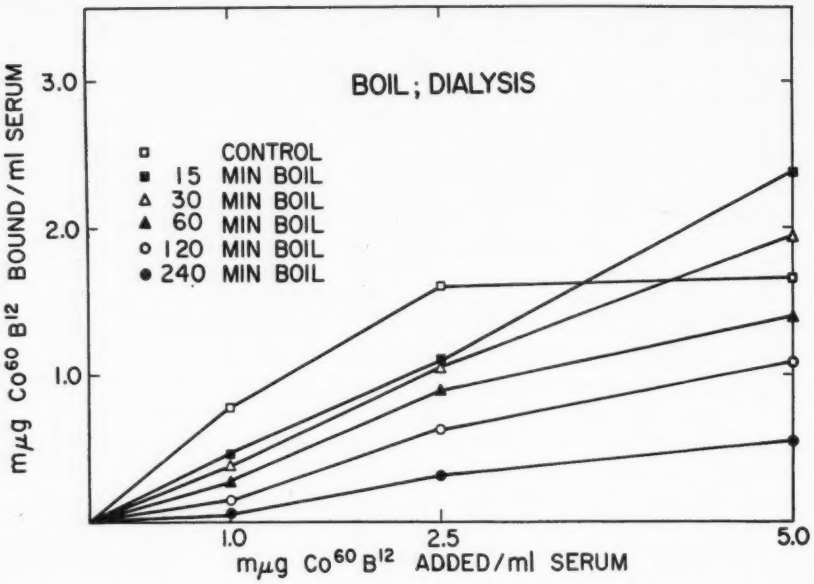

Fig. 2. Effect of heat on serum binding of added Co^{60} B_{12} in presence of excess vitamin.

DISCUSSION

Total binding capacity of normal human serum for vitamin B_{12} exceeds serum content, and is about one mμg/ml (6). When measured by the bioassay methods cited earlier, added vitamin B_{12} has not been regularly recovered when boiling was limited to 15 minutes. By our method, prolonging boiling frees progressively more vitamin B_{12} from protein. Sera boiled 15-30 minutes in the presence of excess vitamin B_{12}, however, bind more of it than do unboiled controls. Whenever sera are boiled in the presence of excess vitamin B_{12}, more is bound than when excess is removed by prior dialysis. Thus some of the vitamin is bound to altered protein.

In serum, vitamin B_{12} is bound specifically to a component of seromucoid and non-specifically to various other proteins (3, 4). This latter fraction may be directly available to microorganisms, accounting for "free" vitamin reported in the serum by bioassay. Vitamin B_{12} which is nondialyzable after 15 minutes boiling is also at least partially available to *Euglena gracilis* (unpublished results), but not entirely so.

After four hours boiling, however, the physicial bond of vitamin B_{12} to protein is broken, and all the vitamin is dialyzable. It is also all available to the bioassay organism. Frederick (2), who got virtually complete recovery of added vitamin B_{12} from sow serum after four hours boiling appreciated this separation, and assayed only supernatant after sedimenting protein. His recovery was most perfect when minute amounts of cyanide were added prior to boiling.

Wolff (8) suggested the effect of cyanide ion was to maintain vitamin B_{12} in the form of heat stable cyanocobalamin, preventing conversion to thermolabile hydroxycobalamin. It has also been suggested that cyanide ion may displace protein or peptide groups linked to vitamin B_{12}. In view of the lack of effect of cyanide on serum vitamin B_{12} binding in our study, only thermal stabilization seems a significant function.

SUMMARY AND CONCLUSIONS

1. Heat denatured serum protein may bind Co^{60} vitamin B_{12} at least as avidly as does native protein.

2. Boiling frees vitamin B_{12} from protein binding in proportion to its duration; complete physical separation of vitamin and protein is achieved after four hours.

3. Cyanide ion in low concentration has no direct effect on the protein-vitamin B_{12} bond.

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Liver Blood Flow and Cellular Function in Hepatobiliary Disease. Tracer Studies with Radiogold and Rose Bengal[1,2]

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INTRODUCTION

The first clinical procedure for estimating liver blood flow according to the Fick principle (1) was described by Bradley in 1945 (2). This method was not widely applied because it required hepatic vein catheterization, repeated blood sampling and continuous bromsulphalein (BSP) infusion. Dobson demonstrated that liver blood flow could be estimated from the blood disappearance rate of P^{32}-labeled chromic phosphate on the principle that small amounts of particulate material are removed from the blood almost exclusively by the liver phagocytes (3). Only repeated samples of peripheral venous blood are required to determine T ½ values with this simplified method. Vetter (4) was the first to use Colloidal Radiogold and external radiation counting techniques to obtain the same information without blood sampling. Later he compared values obtained from Radiogold with those from the BSP extraction technique (5). Gross impairment of blood flow was found in cirrhotics by both methods, and also a direct relation was demonstrated between blood disappearance half-time and increased portal venous pressure. Similar results were obtained by Krook (6) with Colloidal Gold and by Benacerraf (7) who used I^{131}-labeled heat denatured human albumin as the test agent. Baptista and Carvalho (8) preferred to measure the rate of liver accumulation rather than the blood disappearance of Radiogold because smaller amounts of radioactivity could be used and statistically better measurements obtained.

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2. From the Laboratories of Nuclear Medicine and Radiation Biology, the Departments of Biophysics-Nuclear Medicine, Radiology, and Medicine, School of Medicine, University of California at Los Angeles, and the Nuclear Medicine Division of Radiology Service of the Los Angeles County Harbor General Hospital, Torrance, California

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The present consensus of opinion is that blood disappearance techniques are useful in serial studies of portal hypertension for which other methods are impractical (9). However, little information has yet been obtained regarding the influence of impaired blood supply on liver cell function. Such specific liver cell tests as Rose Bengal and bromsulphalein give abnormal values either as a result of cellular damage or of defective blood supply or from a combination of both factors (10), thereby detracting from their diagnostic usefulness. Methods are needed which permit estimation of liver cell function and the extent to which it is impaired by defective hepatic circulation, especially in cirrhosis.

The purposes of this study are: first, to describe the Radiogold and Rose Bengal indices of liver blood flow and cellular function and to present our findings with these tracer tests in a variety of diseases of the liver and biliary tract; second, to demonstrate that the Colloidal Gold liver blood flow index permits accurate evaluation of polygonal cell function with Rose Bengal; third, to indicate the potential usefulness of these two tracer tests in the management of patients with cirrhosis and portal hypertension; and finally, to show their apparent value in the differential diagnosis of severe jaundice, ascites and massive upper gastrointestinal tract hemorrhage.

MATERIAL

The I^{131}-labeled Rose Bengal and Colloidal Au^{198} supplies are available commercially as sterile solutions having relatively high specific activity. These concentrated preparations may be diluted with sterile pyrogen free water or physiological saline to make up individual doses containing the desired amounts of test material and radioactivity. Dilutions to 1:500 do not alter blood disappearance or liver extraction rates of either agent. However, with Radiogold preparations it is essential to keep the dose of colloid below 250 μgm because larger quantities are cleared more slowly from the blood. The rates of blood disappearance and/or liver accumulation of Colloidal Gold in doses up to 250 μgm are the same and have been shown to be indices of liver blood flow (4, 5, 6, 8). However, when this critical dose (250 μgm) is exceeded, blood disappearance T ½ values increase and begin to measure phagocytic capacity of the RE cells, mainly those of the von Kuppfer cells of the liver (7).

Another important factor with Colloidal Gold preparations is their particle size distribution. Supplies from different manufacturers vary considerably in this respect (4, 5). The liver extraction rate is particle size dependent, with small size colloids being extracted more slowly than those having larger mean size distributions (3). Therefore, it is important to use a single supplier who maintains rigid controls in respect to uniformity of production methods and particle size distribution from lot to lot of the same agent.

EQUIPMENT

The arrangement of the gamma-ray scintillation counting and recording equipment now used for measuring both the Radiogold and Rose Bengal blood disappearance-liver extraction rates are shown in Fig. 1. Blood disappearance

is registered continuously following intravenous injection of the tracer from a collimated detector placed over the left side of the head and angled upward away from the chest to minimize scattered radiations from the liver. The 2 inch diameter sodium iodide crystal used in this detector permits accurate measurement of declining levels of radioactivity with tracer doses as low as 5 μc. A similar set of detection equipment is used to register rates of liver extraction of Radiogold and liver extraction-excretion of Rose Bengal. A third set is employed routinely with Rose Bengal studies to determine the intestinal entry time of dye and its rate of delivery from the liver. This third system is also used with Radiogold studies to register rates of accumulation of radioactivity over the splenic area in patients suspected of having hypersplenism.

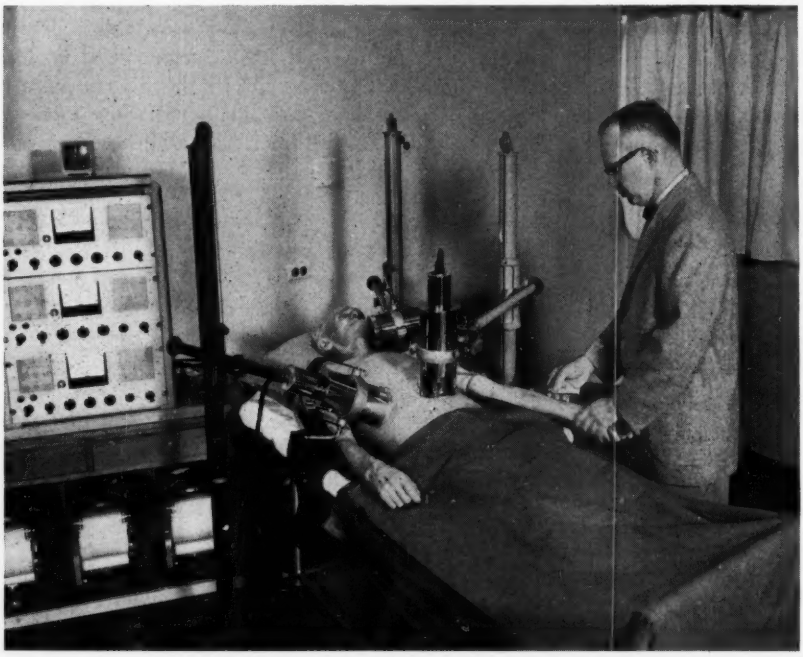

Fig. 1. Arrangement of the gamma ray scintillation counting and recording equipment for performing the Radiogold and Rose Bengal tests.

In the second and third detectors 1.5″ × 1.0″ sodium iodide crystals are used. They have sufficient sensitivity to provide accurate measurements with the small doses used when the crystals are retracted 5 cm. within the collimator of each detector. Reports have been published previously which describe the Rose Bengal Hepatogram techniques, the necessary precautions and the interpretation of abnormal findings (11).

COLLOIDAL Au^{198} TECHNIQUES AND ANALYTICAL METHODS

The techniques for registering the rates of Colloidal Au^{198} blood disappear-

ance and liver accumulation used in this study are basically the same as those previously described by Vetter, et al. (4). Smaller doses of radioactivity (5-10 μc) were permissible in our studies because highly sensitive detection equipment was available. During this investigation forty simultaneous blood disappearance measurements made with one detector placed over the head and the other over the thigh demonstrated that the former gave more consistent and reliable readings. Half-time values recorded from the head were generally less than those obtained from the thigh. Furthermore, only slight differences were found between T ½ values made with several patients in the fasting versus post-prandial states or by testing the same patients in the sitting or recumbent positions.

Considerable attention was given to selecting the most meaningful, reliable and clinically useful method for analyzing Colloidal Gold blood disappearance curves. Most investigators followed the methods set forth originally by Vetter (4) and Krook (6) and plotted the data on semi-log paper. They used the T ½ value for the first exponential phase (1-10 minutes) of the curve after substracting values for the subsequent asymptotic phase. However in our experience, in normal subjects, if the actual linear recording of blood disappearance is extrapolated to zero time by simply excluding the initial spike (bolus effect), this directly registered half-time value is nearly identical to that obtained by the more laborious exponential method. Moreover, half-time values obtained by linear analysis are much greater in patients with proved cirrhosis and portal hypertension than those calculated by the more complicated exponential method, from the same curves. Linear half-time analysis of typical blood and reciprocal liver curves from normal and cirrhotic subjects are shown in Fig. 2. By the linear analysis, the blood T ½ value is 3.5 minutes for the normal subject, and by the original *exponential* method the values for blood and liver curves are 4.0 minutes. However, for the cirrhotic patient, the blood T ½ value is 17.5 minutes by the linear recording and only 7.5 minutes by the exponential method. Thus the exponential method minimizes the estimated impairment of liver blood flow in advanced cirrhosis, which is known to be grossly reduced from direct measurements in animals and from deductions based on the pathology in man (12).

Mathematical analysis of these curves indicates a series of exponential functions (8). Little is known of the physiological basis for these changing slopes other than the bolus effect in the initial phase and the particle size relation (3). The first exponential phase was selected by the original workers (3, 4) because it gave calculated values for blood flow that seemed to fit most reasonably with measured values in animals and estimates with other methods in man (12). We agree that this may be a correct selection and the most scientific method of data analysis; however, until more specific information is obtained relating physiological factors to the various components of the curves, we believe that our simple method for determining half-time values on a linear basis and the use of this value directly as an index of total liver blood flow has merit. Data will be presented in the body of this paper to support this contention.

Furthermore, in our experience with the blood disappearance of Rose Bengal, which does not follow a single exponential function, the same linear method

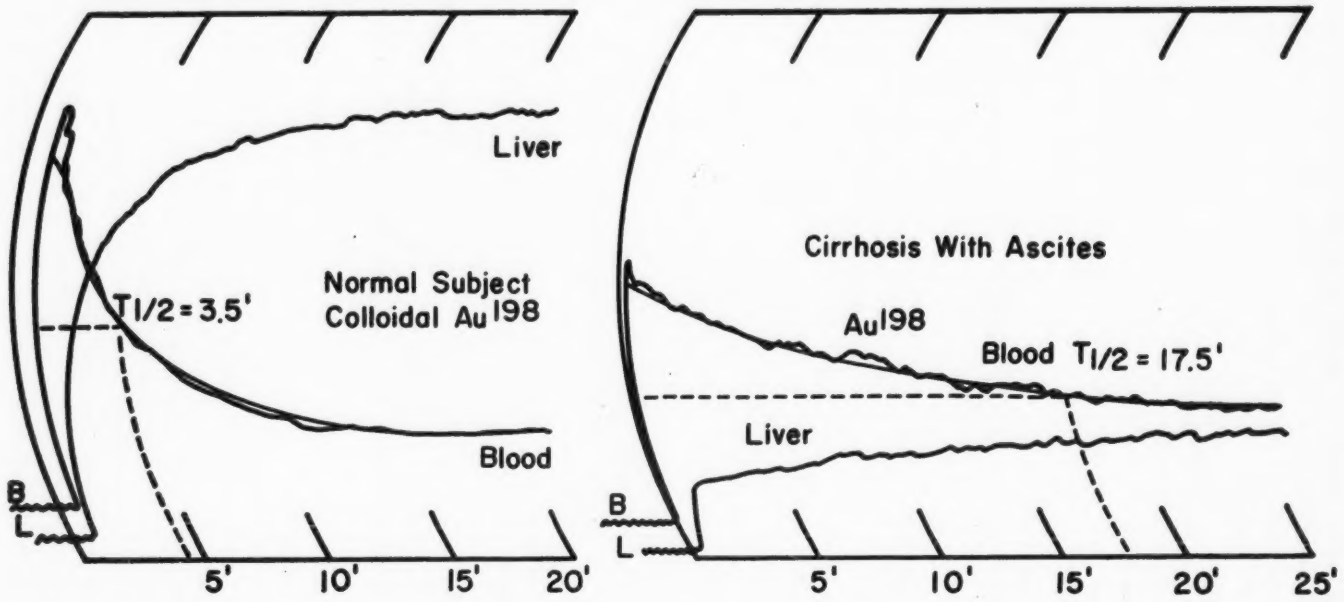

Fig. 2. Typical normal and cirrhotic curves for blood disappearance-liver accumulation, showing the linear half-time analysis method.

of curve analysis has been demonstrated to be superior to other methods for estimating polygonal cell function of the liver (Figs. 3 and 4). By comparison with results obtained with bromsulphalein blood retention in control subjects and in *non-jaundiced* patients with chronic liver disease, the Rose Bengal tracer and stress test findings shown in Figs. 3 and 4 indicate the superiority of half-time measurements over per cent retention by time ratio analysis. These data

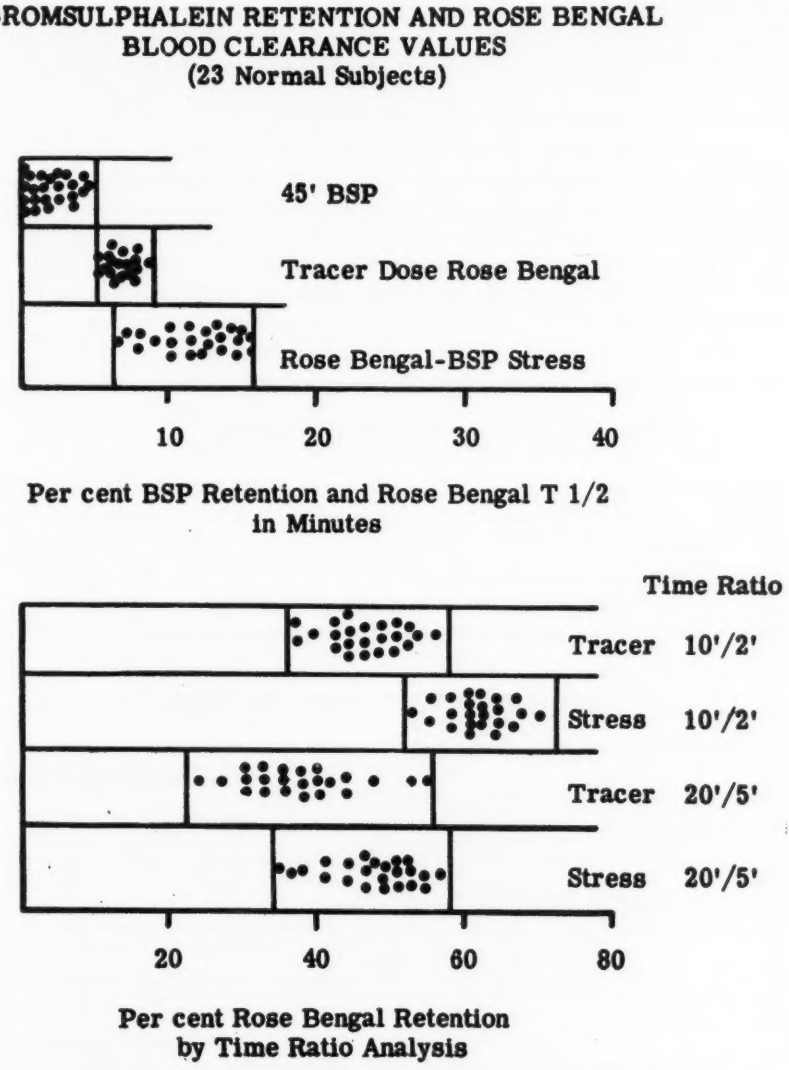

Fig. 3. Bromsulphalein retention and Rose Bengal blood clearance values (23 normal subjects).

also demonstrate that the 45 minutes BSP blood retention test is more sensitive than the tracer Rose Bengal procedure. However, the Rose Bengal-BSP Stress Test has equal or slightly greater sensitvity and the added advantage that it may be performed in 15-30 minutes.

Clinical Material

All patients included in this study had a battery of standard liver tests performed on the same day or within a few days of the Radiogold and Rose Bengal tests. Control subjects were comprised of patients who had recovered from uncomplicated gall bladder operations. All were known to have had normal appearing livers at the time of operation and no physical or laboratory evidence of residual liver damage at the time of tracer testing.

Patients with portal cirrhosis were arbitrarily placed into three main categories: one, decompensated cirrhotics (those with varying degrees of either portal hypertension or liver failure, such as splenomegaly, varices, ascites or hypoproteinemia); two, compensated cirrhotics (patients with proved cirrhosis who had no evidence of liver failure and/or portal hypertensions); and three, post-operative cirrhotic patients who had recovered from side-to-side or end-to-side portal-caval shunt operations for relief of portal hypertension.

Other groups studied included patients with acute infections or serum hepatitis, acute extrahepatic biliary tract obstruction and a miscellaneous group made

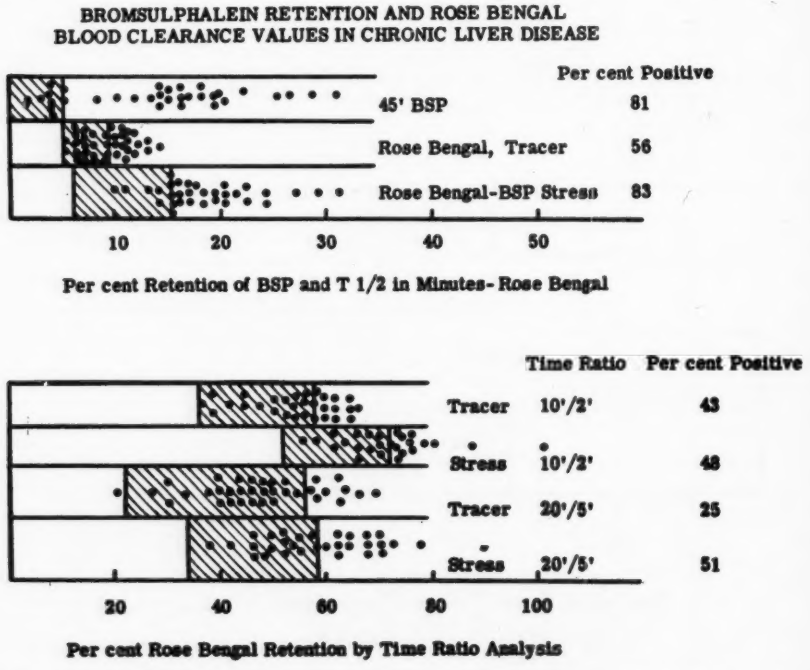

Fig. 4. Bromsulphalein retention and Rose Bengal blood clearance values in chronic liver disease.

up of patients having a variety of diseases not primarily involving the liver, but including many who had unexplained hepatomegaly. In addition, a few patients with congestive heart failure were studied repeatedly during a course of therapy. Patients with severe upper gastrointestinal hemorrhage were tested while in shock and/or after recovery, but while still in a severely anemic state.

Results of standard liver tests obtained in the major groups just described are presented in Table 1. The findings are in accord with the disease classifications presented.

TABLE I. STANDARD LIVER TEST FINDINGS IN GROUPS STUDIED WITH RADIOGOLD AND ROSE BENGAL

		Average Values					
	Number	Albumen (grams %)	Bilirubin (mgms. %)	BSP (45′)	Ceph. Floc. (units)	Thymol T. (units)	Alk. Phos. (units)
Controls	29	4.5	0.6	4.3	±/+	3.8	7
Cirrhosis (Comp.)	19	4.3	1.4	10.9	±/+	5.0	12.0
Cirrhosis (Decomp.)	24	2.9	4.4	30.0	2+/3+	8.0	16.0
Cirrhosis (P. C. Shunt)	11	3.5	2.2	25.0	3+/3+	11.0	14.0
Hepatitis (Acute)	8	3.6	20.4	–	3+/4+	45.0	22.0
Obstructive Jaundice	11	3.8	22.6	–	0/±	4.0	43.6
Miscellaneous	26	4.2	0.8	8.0	+/+	5.0	9.0

RESULTS AND INTERPRETATIONS

Colloidal Radiogold Liver Blood Flow Index

Colloidal Radiogold blood disappearance T 1/2 values are presented in Fig. 5. It is apparent that cirrhosis is the main disease in which an abnormality of liver blood flow is indicated by this method. Moreover, the Au^{198} T 1/2 index of liver blood flow is related to the severity of cirrhosis; only slightly exceeding the normal range in compensated cases and being definitely abnormal in the decompensated and operated cirrhotic groups.

Of equal interest and potential diagnostic value is the failure to find abnormal AU^{198} indices in severely jaundiced patients with acute hepatitis and extrahepatic biliary tract obstruction. Thus it appears that the Au^{198} test has value in the differential diagnosis of severe jaundice. It may also detect underlying cirrhosis in jaundiced patients, as well as in those having ascites and/or massive upper gastrointestinal tract hemorrhage.

Comparison of Au^{198} and Rose Bengal Blood Disappearance Values

Results of *both* tracer tests performed in the same groups of patients are presented in Fig. 6. These data show a relation of 7.5 to 4.5 between mean T 1/2 values for Rose Bengal and Gold in control subjects. The mean values for Rose Bengal and Gold from compensated cirrhotics are slightly greater for both tests but still have a ratio of about 2 to 1, which indicates that the main cause for the positive Rose Bengal indices is impairment of the liver circulation rather than cellular damage. The greater spread in T 1/2 values for Rose Bengal and Gold among the decompensated cirrhotics, a heterogeneous group which included patients having concurrent active hepatitis, recent acute gastrointestinal hemorrhage and acute alcoholism, is indicative of the wide range of damage to both circulatory and cellular functions. The findings in the groups with acute

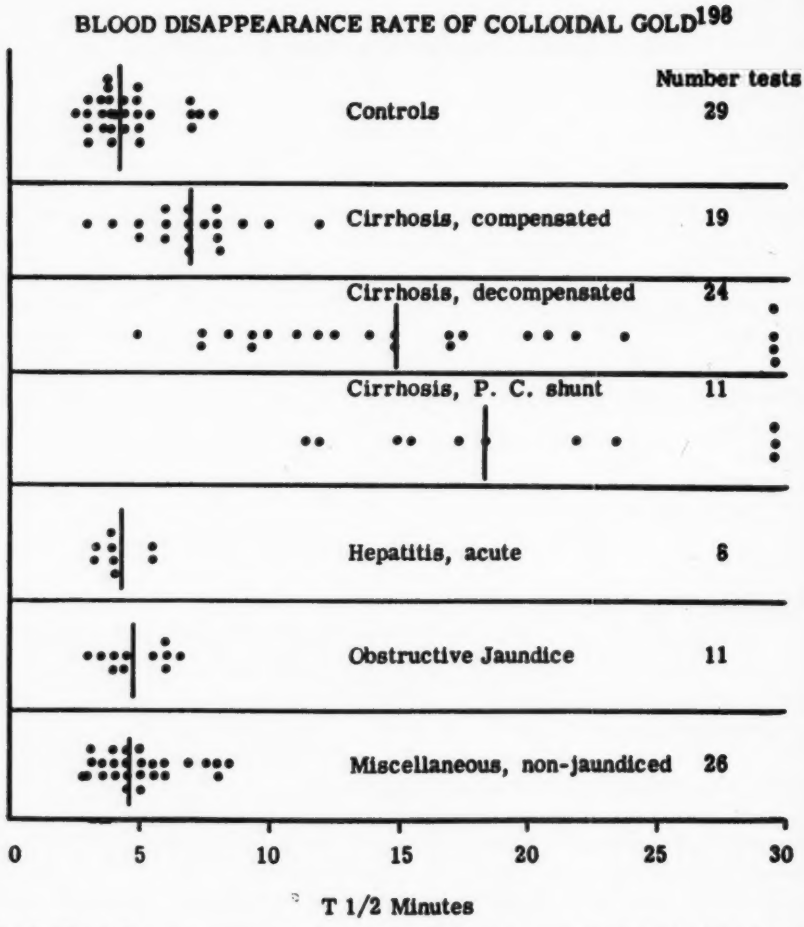

Fig. 5. Blood disappearance rates of Colloidal Gold-198 in control subjects and in hepatobiliary disease.

hepatitis and obstructive jaundice demonstrate that the AU^{198} liver blood flow index is unaffected by severe primary and secondary polygonal cell damage. Cellular injury is reflected in the latter groups by the 6 to 1 and 7 to 1 ratios of Rose Bengal to Gold indices. In these acute conditions, normal liver circulation appears to be maintained in spite of the severe cellular and structural liver injury.

The hepatic circulation is not measurably influenced during the course of severe jaundice from biliary obstruction and does not change following relief of the obstruction and improved cellular function. See Fig. 7 for serial studies in such a case. Likewise, normal liver blood flow is maintained at constant values during the acute phase and early recovery period in acute infectious hepatitis (Fig. 8). In both of the latter cases of jaundice wherein repeated Radiogold and Rose Bengal tests were performed, it is apparent that the Radiogold liver blood flow index was not affected by severe primary and secondary involvement of the polygonal cells, whereas the Rose Bengal indices for liver cell function ran parallel with the fall in bilirubin levels during recovery from both types of liver disease.

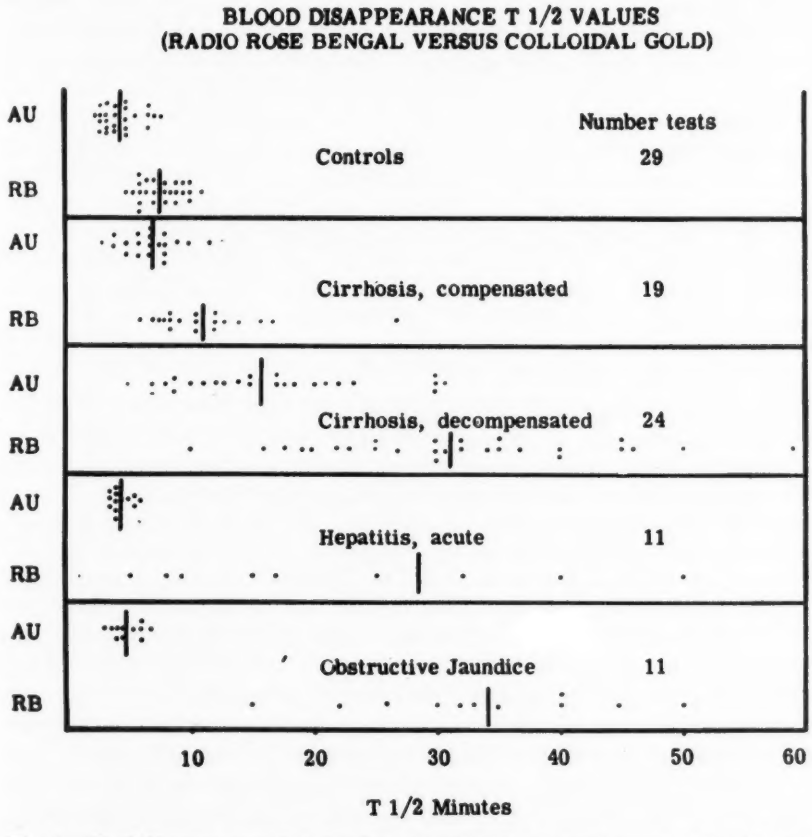

Fig. 6. Blood disappearance T 1/2 values of Radio Rose Bengal versus Colloidal Gold.

By contrast, the impairment of liver blood flow and cellular function occurring in congestive heart failure and hemorrhagic shock has been found to be reversible. Furthermore, when T 1/2 values for both Rose Bengal and Au^{198} are increased (in such vascular disorders), they usually have the normal ratio of 2 to 1 which indicates little, if any, associated liver cell damage. However, when ratios of 3 to 1 or more between Rose Bengal and Gold indices are found in cardiacs, such findings presumably indicate liver cell injury resulting from prolonged venous congestion and associated hepatic hypoxia.

Serial studies of cirrhotic patients recovering from liver failure and ascites usually have shown little or no changes in blood flow, but moderate improvement of cellular functions; a few have shown favorable cellular and circulatory responses to medical management. Additional studies of this type are indicated to determine the conditions and stage of the disease when changes in liver blood flow become irreversible.

Blood Flow and Cellular Function Before and After Surgery

In our limited experience, the Au^{198} liver blood flow test is not greatly altered by either side-to-side or end-to-end portalcaval shunt operations in individuals who have advanced cirrhosis and extensive collateral circulation. This finding is not surprising in view of the fact that such individuals have little functional blood supply from the portal system because of intrahepatic venous obstruction. By contrast, in three patients with moderately severe cirrhosis and portal hypertension, end-to-side operations were followed temporarily by rapid deterioration of liver cell function and further impairment of liver blood flow. Three cases are too few to permit general conclusions, but the findings indicate the need for further studies and possible re-evaluation of present criteria for or against major surgical procedures for the correction of portal hypertension.

DISCUSSION

The value of estimating total functional liver blood flow by the Colloidal Radiogold disappearance method in normal and cirrhotic subjects as previously described by others (4, 5, 6, 8) has been confirmed. The liver blood flow index (the registered blood disappearance half-time in minutes) appears to have equal value and reliability when compared with the more complicated exponential method and also has the advantage of analytical simplicity and practicality in clinical use. The test is especially useful when serial measurements are made in cirrhotics before and after medical and/or surgical treatment. Results of this study have extended the application of the Colloidal Gold index of liver blood flow as an aid in the differential diagnosis of jaundice, ascites and upper gastrointestinal hemorrhage. Further work is needed not only in these new applications, but also in the general field of portal hypertension and chronic liver disease (13).

Our preliminary findings from studying hepatobiliary tract disease with Radiogold and Rose Bengal along with standard methods indicate that impairment of liver circulation and/or cellular function may now be estimated in-

dependently and with accuracy. This is possible because gross damage to the liver cells greatly slows the blood clearance of Rose Bengal but fails to alter the disappearance rate of Colloidal Gold. On the other hand, decreased blood flow, as in cirrhosis, definitely influences the disappearance rates of both Gold and Rose Bengal in relation to the severity of the vascular impairment. Thus, if repeated tracer tests are performed with both agents in cirrhotic patients with associated active hepatitis, one can follow the effect of therapy on cell function with the Rose Bengal index and correct it for the associated vascular effect with the Au^{198} test. Further studies of this type are needed to aid in the development of improved methods of medical and surgical management of cirrhosis and other diseases causing portal hypertension (13).

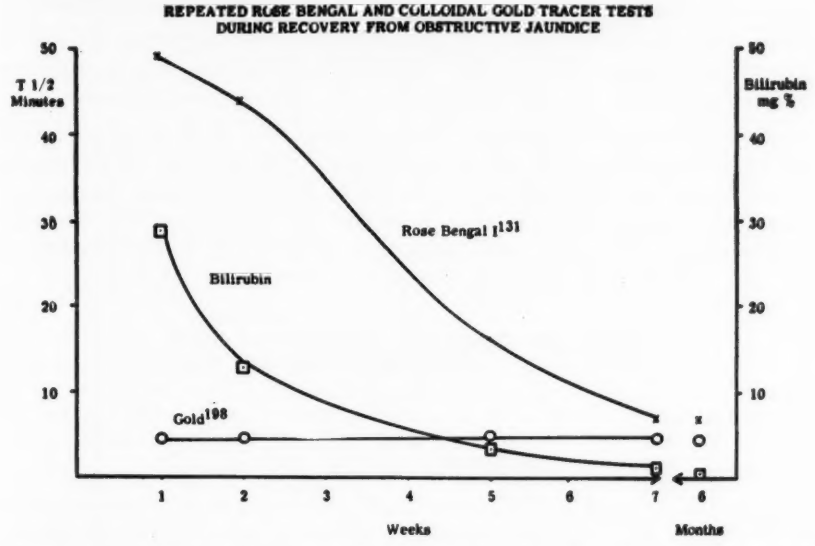

Fig. 7. Repeated Rose Bengal and Colloidal Gold tracer tests during recovery from obstructive jaundice.

There are many unknown factors which may modify the blood disappearance curves not only of colloids, but also of liver cell specific dyes. Some of these are the bolus effect from rapid injection, variations in cardiac output and circulation time, differences in the rates of blood clearance from certain parts of the body, altered rates of dilution and time to reach equilibrium states, the effects of particle size distribution, and finally the influence of disease on many of these factors. While some of these variables are being brought under control by further study, it is suggested that useful information can be obtained from the simple half-time indices of liver blood flow with Colloidal Radiogold and cellular function with Rose Bengal by employing the techniques described in this paper. These simple indices may be further improved by rigid control of the rate of tracer injection, by simultaneous measurement of circulation time and by using adequate amounts of radioactivity to permit accurate measurement of rapidly changing radioactivity levels with the equipment available.

SUMMARY

Liver blood flow and cellular function have been studied in a variety of hepatobiliary diseases with two tracer techniques and by standard methods. The validity of the blood disappearance rate of intravenously injected Colloidal Gold as an estimate of liver blood flow has been confirmed. A simplified method for analyzing such blood disappearance curves has been developed as an index of liver blood flow. The same index (registered blood disappearance T 1/2 values in minutes) is also employed to estimate polygonal cell function of the liver with I^{131}-labeled Rose Bengal, and this index has been shown to be more accurate than other methods of analyzing Rose Bengal curves. The Au^{198} liver blood flow index is positive mainly in cirrhosis and especially in patients with portal hypertension. It is not altered by severe jaundice from either acute hepatitis or biliary tract obstruction. Other conditions which have been found to give a positive Au^{198} index are portal hypertension from lymphatic leukemia, severe congestive heart failure and hemorrhagic shock.

Radiogold and Rose Bengal blood disappearance indices of liver blood flow and cellular function permit independent evaluation of both functions separately and are especially useful in the medical and surgical management of cirrhotic patients with portal hypertension and active hepatitis. The same tests have potential value in the differential diagnosis of severe jaundice, ascites and acute massive upper gastrointestinal tract hemorrhage.

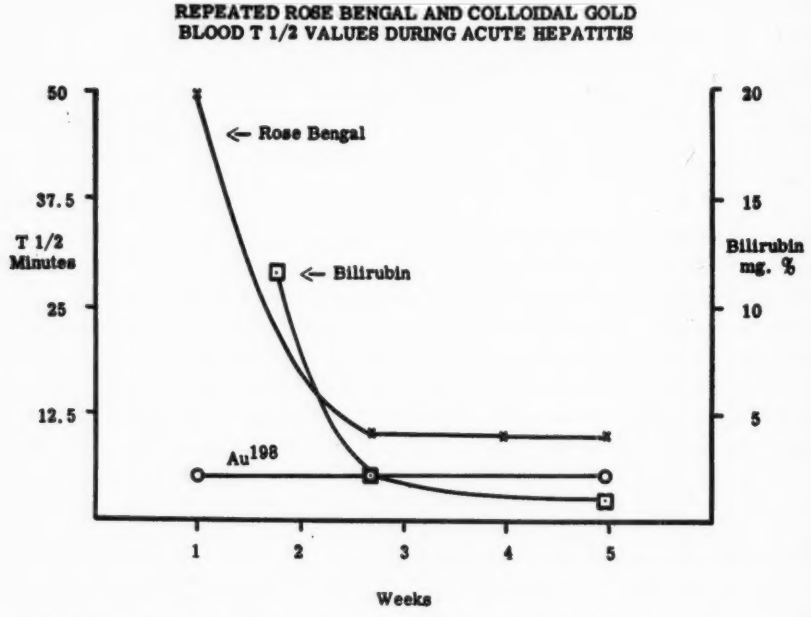

Fig. 8. Repeated Rose Bengal and Colloidal Gold blood T 1/2 values during acute hepatitis.

ACKNOWLEDGEMENTS

We are grateful for the technical assistance of Mrs. Ethel Plummer and for the preparation and standardization of radioisotope supplies by Dr. Raymond Libby and his staff in the Radiology Department at UCLA.

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JOURNAL OF NUCLEAR MEDICINE 2:218, 1961

Effects of Localized Doses of High Intensity X-Irradiation On the Cardiovascular System of the Rat[1]

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Chicago

INTRODUCTION

In order to clarify the effect of localized doses of high intensity x-irradiation on capillary permeability and the cardiovascular system, disappearance curves of radioiodinated serum albumin, arterial pressure, heart rate and rectal temperature were studied in adult male rats before and after very high intensity abdominal and head x-irradiation.

Rigdon and Curl (1) have studied the effect of roentgen rays on the capillary permeability of rabbit skin. They irradiated numerous small patches with doses of from 680 to 2720 r, and injected trypan blue at various times before and after irradiation. The results indicated that any effect on capillary permeability was transient in that there was only a quantitative difference in staining between treated and control skin when the dye was injected one hour following irradiation. If the dye was injected any time after this period there was no difference in the staining characteristics of irradiated and control skin. Painter et al (2) have made *in vivo* observations of blood vessels in the frog's web, and Smith, Svihla and Patt's (3) studies on the vessels in the bat wing showed that radiation is a nonspecific vascular damaging agent. Wish et al (4) determined that labeled homologous and heterologous plasma, and colloidal dyes disappear from the vascular tree of total body irradiated animals faster than from controls. The peak of the response is found in two weeks.

Painter, Prosser et al (2) reported an initial decrease in blood pressure during the first 24 hours following irradiation, even after a total body exposure as

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low as 50 r. According to Toyoma (5), the direction of early blood pressure changes depends on the area irradiated. Irradiation of the cardiac area, midbrain, or the entire head produces a small increase in the blood pressure. Moos et al (6) report a significant increase in heart rate in mice subjected to high intensity irradiation, but possibly this effect is associated with the initial blood pressure response. Patt and Brues (7) feel that the evidence for a generalized circulatory disturbance after median lethal irradiation is not impressive, but point out it may be a factor in relation to massive doses.

METHODS

The investigation was divided into three parts: (1) control animals: treated in every respect as the irradiated animals except that there was no power applied to the x-ray tube; (2) abdominal irradiation: the target skin distance (TSD) over the shaved abdomen was 3.5 cm, 2.0 cm below the ensiform cartilage and directly over the midline of the animal; and (3) head irradiation: TSD 3.5 cm above the shaved head, in the midline at the junction of the frontal and parietal bones. In a separate series of experiments, control and abdominally irradiated animals were subjected to whole body scanning following injection of radioiodinated human serum albumin (RISA) to determine if the albumin accumulated at the point of irradiation.

Adult male rats (200–390 gms.) were anesthetized with sodium pentobarbital administered intraperitonially (4 mg per 100 gm body weight). Ten microcuries of radioiodinated human serum albumin were injected into the saphenous branch of the femoral vein and the amount of RISA remaining in the vascular tree was determined for 160 minutes thereafter. Those animals used for whole body isotope scanning were given 40 to 50 microcuries of RISA intravenously instead of only 10 microcuries. Experimental animals were irradiated with an AEG-50 beryllium window x-ray tube, (45 kv, 40 ma) at a dose rate of approximately 10^5 r per min. All irradiated animals received approximately 2×10^6 r over a 20 minute period. Further details of dosimetry are discussed elsewhere (8).

The left common carotid artery was cannulated, and mean arterial pressure was recorded with a Statham pressure transducer and appropriate amplifying and recording instruments. Heart rate was obtained from this same record. Rectal temperature was recorded visually from a Yellow Springs Instrument Co. Telethermometer. Blood samples for the determination of RISA disappearance were obtained by loosening the joint of the carotid cannula and the three way stopcock, removing the dead space blood, and then allowing a drop of blood to fall on a glass slide. Duplicate samples of 0.01 ml of blood were pipetted into a 75:25 mixture of xylene and brombenzene, and the RISA counted in a Nancy Wood well type scintillation counter. Arterial pressure, heart rate and isotope disappearance records were obtained before and after irradiation, whereas rectal temperature was also recorded throughout the period of x-irradiation.

Isotope scanning was done with a Nuclear Chicago Model 1700 Isotope Scanner, with a focusing collimator and a 2 x 2 inch crystal placed 3.5 cm over the skin.

RESULTS AND DISCUSSION

The results are presented graphically in Figure 1. There was no statistically significant difference (t test for non-paired experiments) in mean arterial pressure, heart rate or rectal temperature between the control and experimental animals. The disappearance of RISA from the vascular tree was, however, significantly different for control versus irradiated animals. This difference appeared in the 10 minutes post-irradiation sample and, except for the 70 minute sample was noted throughout the experiment. These results are consistent with the autopsy findings which indicated marked vascular damage in the irradiated area. This was especially evident in the abdominally irradiated group where autopsy findings included marked distention of the gut, hemorrhagic intestinal mucosa, and an accumulation of fluid in the peritoneal cavity.

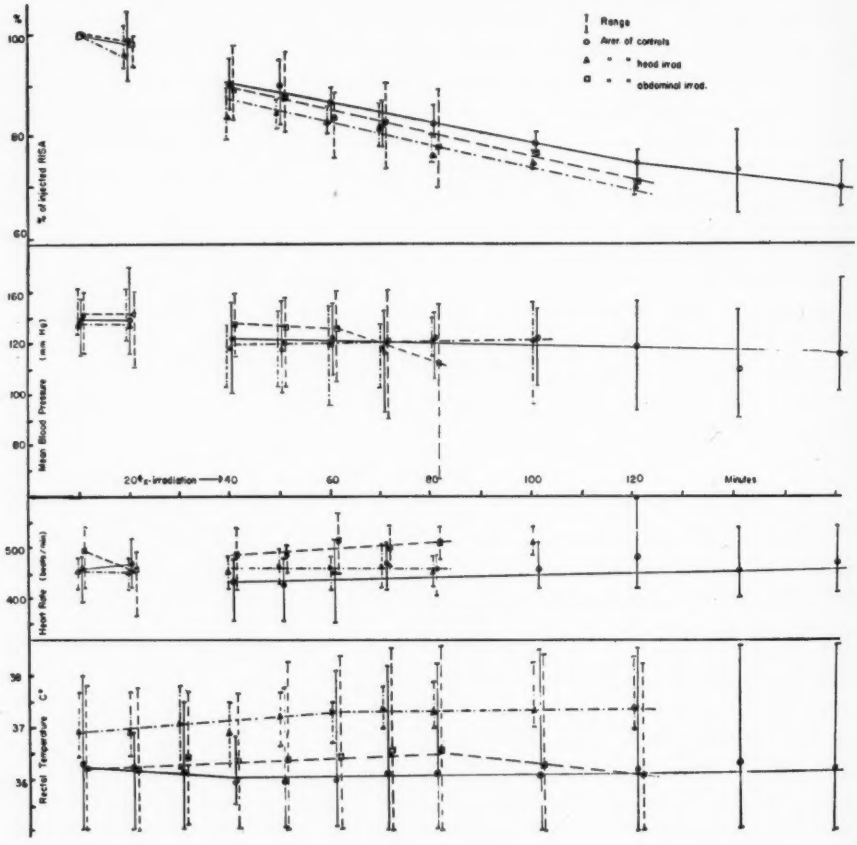

Fig. 1. a. RISA disappearance curve
b. Mean blood pressure
c. Heart rate
d. Rectal temperature

Further evidence for the localized accumulation of RISA in the area x-irradiated at high intensity was obtained by whole body scanning following the intravenous injection of large doses of RISA. Typical control and experimental scanning records are presented in Figure 2. It is seen that there is a definite accumulation of RISA in the localized area of irradiation, and this accumulation continually increases up to the time of death of the animal. In order to determine that the vascular changes resulting from x-irradiation were not simply due to the heat generated by the x-ray tube, animals were subjected to a heat lamp producing comparable temperature changes in the same area of the abdomen as x-irradiated animals. Similar scanning records were obtained with control and heat treated animals. The fact that neither statistically nor physiologically significant changes in rectal temperature were obtained in control or experiment animals further emphasizes the fact that heat per se was not a significant factor. It therefore appears that the amount of x-irradiation used in these experiments is sufficient to cause severe vascular damage in the localized area of irradiation. The disruption of capillary integrity was not only intense enough to be visible on gross examination as well as causing an accumulation of RISA in the localized area, but also was of sufficient severity to produce a detectable change in the over-all disappearance of RISA from the vascular tree. It is questionable whether the x-irradiation produced an increase in capillary fragility, that is, a disruption of the integrity of the capillary membrane as suggested by McCutcheon (9) or simply increased the capillary permeability which implies penetration through an intact capillary wall.

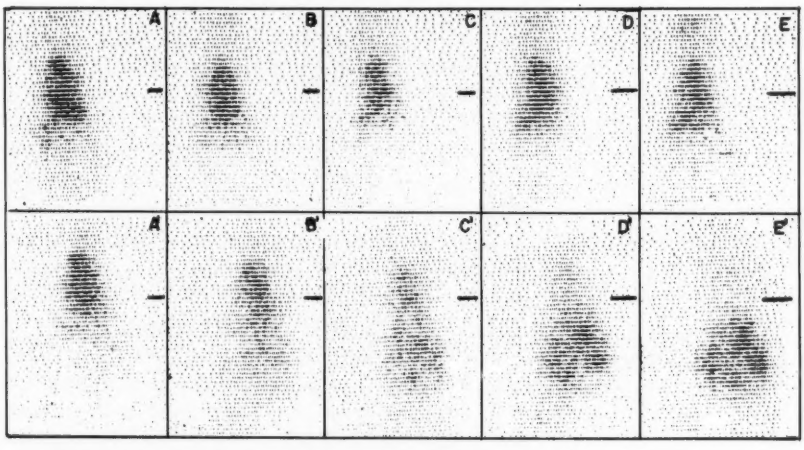

Fig. 2. Whole body scanning records of RISA injected rats

Control (top row) Abdominal irradiation (bottom row)
A'—before irradiation
B'—10 minutes after irradiation
C'—90 " " "
D'—180 " " "
E'—300 " " "
Mark on right hand side of each record indicates level of ensiform cartilage.

The changes in blood pressure and heart rate were not statistically significant when controls were compared to x-irradiated animals. This may be accounted for by pressoreceptor reflexes within the aortic arch and carotid bodies which tended to maintain these parameters at optimal levels even though significant amounts of fluid were being lost through the irradiated area. Thus, significant changes did not occur until the animal was very near death.

SUMMARY

Localized doses of high intensity x-irradiation produce marked changes in the vascular network of the irradiated area. These changes are severe enough to: 1) be visible on gross examination at autopsy, 2) cause accumulation of RISA in the localized area, and 3) cause a statistically significant loss of RISA from the vascular tree in general, thereby indicating an increase in capillary fragility or permeability. Changes in blood pressure and heart rate in irradiated animals were not significantly different from controls, but this can be accounted for by pressoreceptor reflexes which tend to maintain these parameters at physiologically optimal levels.

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In Vitro Labeling of Proliferating Tissues and Tumors With Tritiated Thymidine[1,2]

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INTRODUCTION

The availability of the DNA precursor, tritiated thymidine, (H^3TDR), has made it feasible to study the kinetics of cellular proliferation by high resolution microautoradiographic techniques (1-5).

Various studies with H^3TDR have generally utilized parenteral injection of H^3TDR into selected human patients and various animals followed by serial sampling of tissues for autoradiographic evaluation of labeled cell nuclei. A single parenteral injection produces a "flash labeling" of proliferative tissues due to the rapid incorporation of the H^3TDR into new DNA and its short availability time (4). From an autoradiographic study of the "flash labeling", the appearance of labeled cells in nonproliferative compartments and the diminution in the intensity of the label with time one can estimate various time parameters of the generative cycle (6, 7).

These *in vivo* studies have yielded considerable new information on cell turnover and fate of selected proliferating tissues; however, this type of study has required millicurie amounts of this relatively costly compound. Also, H^3TDR administration to human beings has been restricted to studies in non-procreative patients with short life expectancies because of the inherent difficulties in dose calculation and potential genetic hazard (7-9). In the studies presented here, a modification of the *in vitro* labeling procedure (2) has been applied to normal and neoplastic tissues. Labeling of proliferating cells in diverse tissues was achieved. Advantages and results will be discussed.

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2. Research supported by the U. S. Atomic Energy Commission and National Cancer Institute, Public Health Service (C-5325).

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MATERIALS AND METHODS

H^3 thymidine was received in concentrations of 1 mc/ml at a specific activity of 1.9 C/mM.[1] Dilutions of this stock solution were made in physiological saline and aliquots deep-frozen or refrigerated at 4° C. The diluted solutions were stable and remained capable of labeling DNA after storage for 2 months.

The *invitro* incubation mixtures varied in these preliminary efforts in order to evaluate the necessity of various components and will be described for each tissue. In general, the fresh tissue was cut into small pieces and added to a diluent (which consisted usually of Ringer's lactate) and H^3TDR (1.9 C/mM). After mixing, the tissues were incubated for one hour at room temperature then removed and fixed in buffered formalin. After fixation they were thoroughly washed in running water and paraffin blocks prepared. Thin (4 micron) sections from the first 3 cuts were placed on slides and deparaffinized. Smears of cells were dried and fixed in methanol for 10 minutes.

Autoradiographs (ARG) of the slides were prepared using Kodak AR-10 stripping film and Kodak NTB-3 dipping emulsion. Exposure times were arbitrarily varied depending upon the tissue studied and are listed. Development and staining of the ARG has been described earlier (2). Harris hematoxylin stain was used for tissues and Giemsa or May-Gruenwald Giemsa for smears.

The ARGs were examined by oil immersion microscopy and the labeled cells identified by black silver grains overlying their nuclei. Cells were considered labeled if there were 5 or more grains above their nuclei. The background was low and randomly scattered.

RESULTS

Tonsils:

Tonsils were studied in 4 adults and 4 children who were afebrile at the time of tonsillectomy and whose tonsils had no visible exudate. Small pieces of tonsillar tissue about 3 x 2 mm were added to incubation mixtures consisting of 7 ml Ringer's lactate and 2 ml of pooled normal human serum. Twenty or 100 μc of H^3TDR were added. After mixing, the tissues were incubated at room temperature for 60 to 90 minutes and then ARG of smears and sections prepared. An example of labeling of tonsils is shown in Fig. 1A. This is a smear ARG from the tonsil of a 4 year old boy after 3 weeks exposure. Extensive labeling of lymphoblasts and large lymphocytes is seen. Small lymphocytes were not labeled. Of the larger cells 17 of 205 were labeled producing a labeling index, L. I., of 8.3 per cent.

ARG of sections of the tonsils produced poorer preparations due to shrinkage by, fixation with resultant crowding and the unavoidable superimposition of nuclei in a 4 micron section. However, numerous labeled cells were seen in every case after an exposure of 3 weeks.

The high labeling index of tonsillar tissue is apparent from the photograph. This readily accessible lymphocytic tissue is obviously actively proliferating under the conditions existing prior to tonsillectomy.

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1. Schwarz Bioresearch, Inc., Mt. Vernon, New York.

Intestinal Mucosa:

The "steady state" proliferation of the gastrointestinal tract has been demonstrated by *in vivo* studies using H^3TDR (10, 11). The proliferative capacity can be demonstrated by *in vitro* studies on biopsies of intestinal tract. Canine ileum was well labeled *in vitro* after immediate removal of a 2 cm segment from a dog killed by barbiturate anesthesia. The piece of ileum was washed in saline, incubated in 10 ml of a solution containing 100 μc of H^3TDR per ml, 20 per cent pooled normal human serum and 80 per cent of a balanced salt solution for 60 minutes, fixed, and autoradiographs prepared as described earlier. After two weeks exposure extensive labeling of cells was seen in the crypts of Lieberkuhn indistinguishable from that seen after *in vivo* "flash labeling" of the small bowel.

An application of this technique in human disease is shown in Fig 1B showing an ARG of an intestinal biopsy from a patient with sprue to be reported in detail elsewhere.[1]

Rat Kidney:

It has long been known that unilateral nephrectomy in the rat will produce hypertrophy of the remaining kidney. *In vitro* labeling by H^3TDR was performed on the remaining kidneys of three Wistar rats at 2, 5 and 9 days after unilateral nephrectomy and on the first kidneys removed at the initial operation. Three mm slices of the kidneys (about 0.5 gm) were incubated for one hour in 10 ml of Ringer's lactate containing 2 μc of H^3TDR per ml. After formalin fixation, sectioning, and six weeks of exposure using AR-10 stripping film, clear labeling of proliferating tubular cells was obtained from the first kidneys removed at operation. After 2, 5 and 9 days renal hypertrophy had developed in the remaining kidney and they were similarly labeled *in vitro*. At these time intervals the fraction of cells labeled appeared slightly increased but was not impressive nor statistically significant in these preliminary studies.

Human Tumors:

Biopsy specimens were obtained at surgery and promptly added to the incubation mixtures. In Table 1 are shown the tumor diagnoses, the incubation mixtures used, the exposure times and types of films used. Cell counts of labeled and unlabeled cells and the per cent of cells labeled, L. I., are also listed in Table 1.

In a mucinous cystadenocarinoma 37 of 6000 cells were labeled (L.I. = 0.6%). In an amelanotic melanosacroma 7 of 6000 cells were labeled (L.I. + 0.1%). In an astrocytoma 4 cells in 6000 were labeled (L.I. = 0.07%). Mitoses were rare and none were labeled.

Labeled tumors have yielded an observation which complicates interpretation of these studies. So far 5 small focal areas of proliferation involving 4-5 labeled cells have been seen in the mucinous cystadenoma and one focal area in

1. Obtained in collaborative study with Major Milton Rubini (MC) USA and Captain Thomas Sheehy (MC) USA at the USA Tropical Medicine Research Laboratory, San Juan, Puerto Rico.

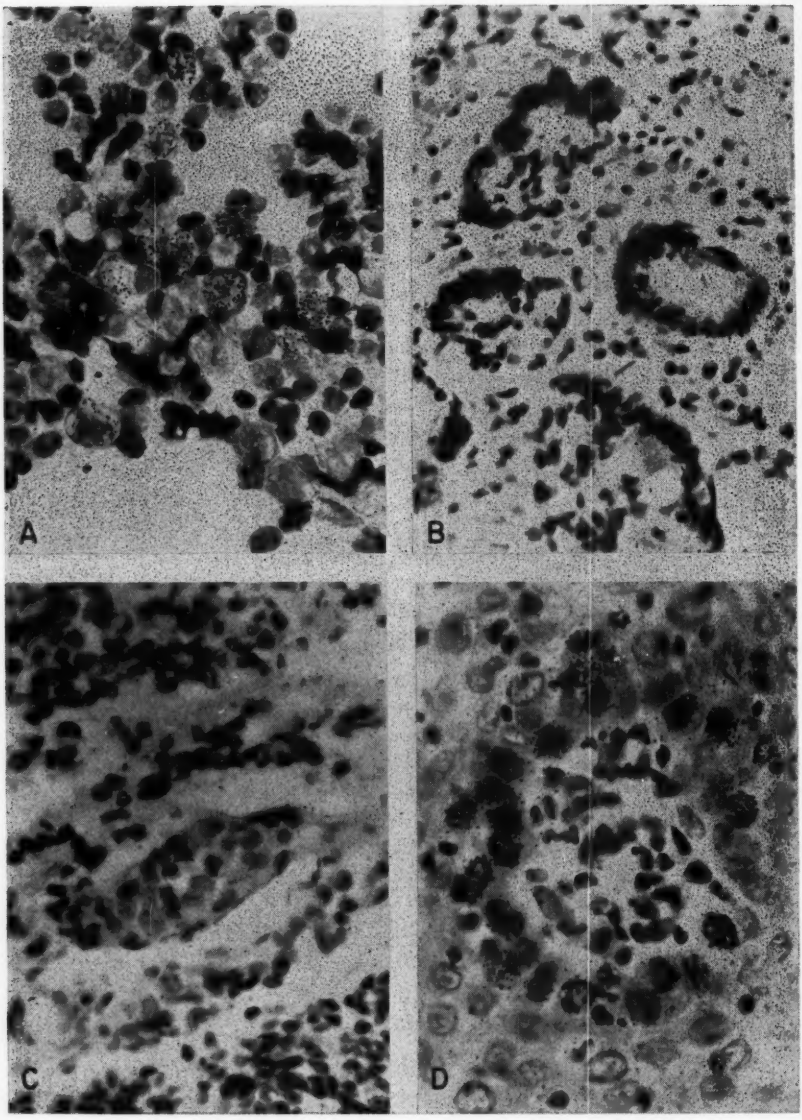

Fig. 1. ***In Vitro*** **Labeling of Tissues and Tumors with H^3 Thymidine**

A—Children's tonsil
B—Small intestinal biopsy in sprue
C—Amelanotic melanosarcoma
D—Squamous cell carcinoma of skin (face)

the melanoma as seen in Fig. 1C. These labeled "nests", if characteristic of tumors, will introduce a non-random factor into all studies on neoplastic cell proliferation with H^3TDR which may bias analysis. A squamous cell carcinoma of skin revealed clusters of heavily labeled cells surrounding the corium in the stratum germinativium as shown in Fig. 1D.

DISCUSSION

In vitro incubation of fresh tissues and tumors with H^3TDR for one hour results in labeling of those cells of the population that were actively synthesizing DNA. The technique permits a wide variety of human and animal tissues and tumors to be studied and should yield new information on their proliferative potentials under numerous conditions. The method requires small amounts of H^3TDR and permits repeat biopsies to be made at various time intervals.

There are, however, certain disadvantages and limitations of this *in vitro* method that require further improvement and impose certain limitations. While Ringer's lactate is a suitable diluent, the amount of H^3TDR needed is less certain. It appears that 1 μc/ml of solution should usually suffice. When larger amounts of H^3TDR are used it may be possible to reduce the exposure period (12). When gastrointestinal mucosa is incubated it seems prudent to use more H^3TDR because of the presence of thymidine phosphorylase (12) in the mucosa which might competitively degrade the H^3 thymidine. The amount of H^3 activity taken up by the tissues is very small and we have not detected any consistent significant difference in the tritium activity of the incubation mixture supernates before and after the one hour incubation period during which cell labeling occurred. However, some of the remaining activity represents other tritiated compounds which are no longer available for DNA labeling. The "used" incubation mixtures contained unchanged non-volatile H^3 activity but these supernates fail to label fresh tissues (12).

The *in vivo* metabolic studies of injected H^3TDR in patients (4) show that H^3TDR leaves the circulation rapidly during the first perfusion cycle and is thereafter rapidly metabolized to tritiated water, non-volatile tritium compounds or incorporated into DNA. If phosphorylated extracellularly to its nucleotide it is not able to gain access to the cells and be incorporated into DNA. Similarly, if reacted with nucleoside phosphorylase, the H^3 thymine liberated is less likely to be utilized for DNA synthesis. The rapid increase in percent labeling and grain counts over basophilic normoblasts of bone marrow in the first few minutes following a single injection of H^3TDR *in vivo* (4) further demonstrates that the "effective labeling" period is about 20 minutes and the labeling process is essentially completed within one hour. We have noticed that when unlabeled TDR is added to H^3TDR and marrow cells *in vitro,* decreased labeling by dilution is only obtained when the unlabeled compound is added from 0 to 20 minutes. When cold TDR is added after 20 minutes, no decrease in labeling occurs (12).

It is logical to assume that H^3TDR will diffuse into bits of tissue in accordance with diffusion laws and one should expect the labeling achieved in all instances to be similar to *in vivo* "flash labeling". However, it has been shown that only the first few cell (100 u) layers of pieces of tissue label (13). In an

TABLE 1. TUMORS LABELED *in vitro* WITH H^3 THYMIDINE

Tissue	*Incubation Mixture and Time*	*H^3TDR*	*Exposure*	*Total Cells Counted*	*Labeled Cells*	*Per Cent Labeled*
Amelanotic melanosarcoma	5 ml. PVP (3.5%) 1 hr. at rm. temp. (25°C)	4 μc	3 weeks NTB–3	6000	37	0.6
Mucinous cystadenocarcinoma of the colon	Ringer's Lactate —7 ml. Serum (pooled human)—2 ml. Penicillin —10000u Streptomycin —50 mgms. 4°C 1½ hrs. then 37°C 1½ hrs.	16 μc	2 weeks NTB–3	6000	7	0.1
Astrocytoma	Same as above	16 μc	2 weeks NTB–3	6000	4	0.07
Squamous cell carcinoma of the skin (face)	Hank's Solution—8 ml. 4°C—1 hr. then 37°C—2 hrs. with shaking	25 μc	6 weeks AR–10			

ttempt to permit deeper diffusion of the H^3TDR into tissues, the incubation nixtures were refrigerated overnight at 5° C which prevents DNA synthesis. Jpon warming to 37° C DNA synthesis commences again. However, labeling till occurred only in the first 100 u; hence there is no advantage in refrigerating issue to permit deeper diffusion of H^3TDR.

In these studies only the first three outer 4 micron sections (12 microns) vere studied, thus a fair approximation of *in vivo* proliferative potentials has probably been attained since it has been shown that the first 100 microns are atisfactorily labeled (13). Prolonged incubation for periods of greater than one iour should in principle allow further cells to enter DNA synthesis and progressively increase the L.I. However, empiric tests of this in our laboratory and by Brecher (14) have not shown any significant increase in L.I. over a 4 hour period. Either cells do not enter DNA synthesis in this *in vitro* system or the H^3TDR is altered so that it can not label DNA after a short while (phosphorylization, degradation, etc.) Bond et al (15) have compared *in vivo* "flash labeling" of bone marrow with *in vitro* labeling and found a striking similarity. Thus when there are small thin pieces of tissues or cell suspensions the *in vitro* method approximates the *in vivo* "flash labeling" and permits a fairly reliable index of proliferative potentials.

The studies on tumors reported herein confirm the *in vitro* and *in vivo* studies performed earlier (2, 6, 16-18). Tumor and tissue growth has been estimated in the past by size measurements and by histological appearance (19, 20) largely based on presence of mitotic figures which are notoriously difficult to find unless special methods are utilized. The advent of H^3TDR appears to offer a new method of assessing tissue growth based on the number of labeled muclei seen. In general, rapidly growing tissue might be expected to have a high labeling index and in contrast a tissue with a slow turnover rate will be rarely labeled. *In vitro* labeling of tissues with H^3TDR therefore should permit repeated evaluations of labeling to be made with relatively little cost and hazard to the patient. This added parameter, the DNA labeling achieved, should augment classical techniques and yield further information on tissue and tumor growth and as affected by various therapies.

SUMMARY

1. Human and animal tissues and tumors were incubated *in vitro* with H^3 thymidine.

2. Proliferating cells of these tissues incorporate the H^3 thymidine into new DNA.

3. Autoradiography of prepared tissue sections revealed excellent labeling of proliferating cells with this *in vitro* method.

4. Some advantages and disadvantages of *in vitro* cell labeling are discussed.

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An In Vitro Procedure for Screening Intrinsic Factor Concentrates[1,2]

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INTRODUCTION

Intrinsic factor (IF) which is essential for the absorption of physiological amounts of vitamin B_{12} has not yet been isolated in pure form; therefore, a biological assay method to demonstrate its presence and to quantify its potency must be used. This has become of increasing importance because of the widespread use of hog intrinsic factor concentrate (IFC) in the diagnosis and therapy of pernicious anemia (PA), as well as in the investigation of vitamin B_{12} absorption. For many years, the standard procedure used to assay IFC was the one described in the U.S.P. (1) which required a satisfactory reticulocyte response in three PA patients in relapse. Following the synthesis of radioisotope labeled vitamin B_{12}, a more reliable and more easily accessible technic for the measurement of vitamin B_{12} absorption became available. Such a technic has been in successful use for several years in the form of the so-called "Schilling test", which at present is the most reliable and most practical test for the diagnosis of PA. The National Formulary's Anti-Anemia Products Committee, realizing the possibilities of this method for an IFC assay, as shown by Williams and Ellenbogen (2) and others (3, 4), has directed that all IFC sold in this country shall be assayed by a modification of the Schilling test beginning on January 1, 1961 (5).

This new standard method of assay removes the necessity for the PA patients to be in relapse; however, it requires the cooperation of such patients and the

1. From the Radioisotope Service and Medical Service, Veterans Administration West Side Hospital, and the Department of Medicine, University of Illinois, College of Medicine, Chicago.

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administration of a radioactive preparation to human beings. The extensive experimentation in the development of a potent product suitable for human use may require the testing of many IFC's before the most satisfactory one is found. To assist in identifying those IFC's that may give promise for human use, a screening procedure would be of value. Several investigators have proposed IFC assay procedures not requiring the cooperation of patients. An attempt to use gastrectomized rats for this purpose was unsuccessful because of the fact that hog IF does not enhance the absorption of vitamin B_{12} in the rat (6, 7). Measurement of IF binding of vitamin B_{12} by dialysis (8) and microbiological assay (9) has proved to be unsatisfactory (10, 11). More recently, Barlow (12) has suggested the utilization of electrophoretic fractions of the Co^{60}-B_{12} IF complex as an assay procedure.

Following the demonstration that rat liver slices (13, 14, 15) and rat liver homogenate (13, 14) bind radioactive vitamin B_{12} when incubated with IFC, Miller and Hunter (16) and Minard and Wagner (17), have suggested that this phenomenon could be utilized for IF assay. It is the purpose of this report to add supporting evidence that an *in vitro* system of rat liver–hog IFC may be used for the quantitative assay of IF.

MATERIALS AND METHODS

The seven hog IFC's used in this study were supplied by the Wilson Laboratories, Chicago, Illinois. The standard concentrate and the concentrates D, E, G (Table 1) were prepared by extraction technics while the preparations A, B, C were obtained by chromatographic purification of the standard preparation. All these IFC's contained less than 0.1 μg per cent of vitamin B_{12} and were of varying potency. They were assayed by 3 methods. 1) a modified Schilling test performed in 2-5 patients, 2) incubation of rat liver homogenate with IFC followed by incubation with Co^{58}-B_{12} ("sequential" technic), and 3) incubation of rat liver homogenate with a mixture of IFC and Co^{58}-B_{12} ("simultaneous" technic). The methods 2 and 3 are modifications of techniques suggested by Herbert (18,

TABLE 1

EFFECT OF VARIOUS IFC'S ON THE PER CENT URINARY EXCRETION OF CO^{58}-B_{12} IN PA PATIENTS

Name	*No IF*	*30 mg Std.*	*6 mg A*	*15 mg B*	*6 mg C*	*30 mg D*	*30 mg E*	*30 mg G*
Mau	1.9	7.4	25.4	17.2	2.7	8.0	5.9	3.8
Bry	0.6	5.2		20.9		12.0	9.5	5.5
Mis	1.6	4.1			8.2	6.9	3.7	2.9
Cla	1.7	2.6		21.0				
Col	1.4	6.0	16.9					
Rank[a]		VI	I	II	III	IV	V	VII

[a] Calculated by methods suggested by Best (20).

19). The standard IFC with which the others were compared has been shown to be fully active by the classical reticulocyte response of PA patients at a daily dose of 10 mg together with 15 μg vitamin B_{12}, and also by the Schilling test.

A modified Schilling test consisting of the oral administration of 0.5 μg Co^{58}-B_{12} to known PA patients followed two hours later by an intramuscular injection of 1 mg vitamin B_{12} ("flushing dose") was used. Urine was collected for 24 hours following the oral dose, and the percent of Co^{58}-B_{12} excreted was determined with a scintillation well counter. The same procedure was repeated with the addition of IFC. The dose of IFC was 30 mg for the standard preparation and the concentrates D, E, G; 15 mg for concentrate B; 6 mg for concentrates A and C (Table 1). The lower dosage of the IFC's A, B, C was used because of their expected higher potency and the limited supply. The potency of each IFC was determined by comparing its capacity to enhance urinary Co^{58}-B_{12} excretion with the enhancement achieved by the standard IFC. Because of the different dosage of the IFC's direct comparison was not possible and mathematical methods suggested by Best (20) were applied (Table 2). In these calculations the possibility of a logarithmic or linear dose response was considered.

TABLE 2

IFC ASSAY IN VIVO AND IN VITRO

IFC	*Urinary Excretion Test*		*"Simultaneous" Incubation*		*"Sequential" Incubation*	
	Relative Potency[a]	*Rank*	*Relative Potency*[b]	*Rank*	*Relative Potency*[c]	*Rank*
Superior						
A	12, 19	I	6	I	0.1	VI
B	5, 19	II	4.3	II	0.08	VII
C	5, 7	III	3.5	III	0.2	V
D	1.2, 1.7	IV	2	IV	0.6	IV
Std. Equiv.						
E	1.1, 1.1	V	1.1	V	1.7	I
Std.	1, 1	VI	1	VI	1	III
Inferior						
G	0.9, 0.6	VII	0.8	VII	1.3	II

[a] The first figure was obtained by assuming a logarithmic and the second figure by assuming a linear dose response (20).

[b] Relative potency $= \dfrac{\mu\text{g standard IFC at maximal } Co^{58}\ B_{12} \text{ binding}}{\mu\text{g IFC at maximal } Co^{58}\ B_{12} \text{ binding}}$ (Fig. 2)

[c] Relative potency $= \dfrac{\text{slope of IFC curve}}{\text{slope of standard IFC curve}}$ (Fig. 1)

The *in vitro* tests were performed on liver homogenates from Sprague-Dawley rats weighing 200-400 gm which had been decapitated, exsanguinated and their livers removed. Liver homogenate, buffer, (containing K 111, Mg 20, Ca 10, Cl 168 and PO_4 4mM/liter), Co^{58}-B_{12} and IFC solutions were prepared as suggested by Minard and Wagner (17) with the exception that 0.025 μg B_{12} was added to each flask in 0.5 ml isotonic KCl instead of 0.018 μg B_{12} in 0.2 ml isotonic KCl.

The "sequential" procedure (Method 2) was performed by incubating 1 ml of homogenate with varying quantities of IFC and with 2 ml of buffer solution for one hour at 0°-4° C[1] in air followed by a single washing with 4 ml of isotonic KCl, and then re-incubating with Co^{58}-B_{12} and 2 ml of buffer solution for a second hour. Following the second incubation, samples were washed twice with isotonic KCl and counted in a scintillation well counter. The "simultaneous" procedure (Method 3) was performed identically to that above except that the liver homogenate was incubated in a mixture of IFC and Co^{58}-B_{12} for two hours without a second incubation.

In both *in vitro* procedures, the amount of Co^{58}-B_{12} retained in the liver homogenate following incubation and washing was expressed as a per cent of the initial amount. Blanks containing no IFC were run during each experiment, and the net IFC effect calculated. In addition, a sample of the standard IFC was tested in each experiment at one or more levels to act as a control. The determination of the relative potency of the IFC's in these *in vitro* procedures will be discussed in the following section.

RESULTS

The results of the modified Schilling test for the seven IFC's are listed in Table 1, and a rank has been assigned to each IFC according to its relative potency.

Pre-incubation of the liver homogenate with IFC prior to the addition of Co^{58}-B_{12} ("sequential" technic) resulted in a dose-uptake relationship which was different for each IFC (Fig. 1). These curves were linear from about 150 μg to 750 μg of IFC. The slope of the linear portion of each curve was used to compare each IFC with the standard (Table 2). When liver homogenate was incubated with a mixture of IFC and Co^{58}-B_{12} ("simultaneous" technic), the resulting curves showed a peak value followed by a rapid decline (Fig. 2). To determine the relative potency of the IFC's either the initial slope (17) or the number of μg of IFC needed to achieve "peak values" on the curve (19) can be compared with the respective values for the standard preparation. In Table 2, the IFC's are ranked by comparing the "peak values" based on the assumption that the smaller the amount of IFC to achieve "peak values", the more potent was the IFC.

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1. This temperature was chosen because of Herbert's (19) findings that at this temperature, IFC maximally enhances the net uptake of vitamin B_{12} by liver slices. According to our findings, this also appears to apply to liver homogenate.

Each curve for both the "sequential" and "simultaneous" methods (Fig. 1 and 2) was constructed from the data of 2 to 5 experiments with each point on the curve representing the mean of at least three determinations. For 500 μg of *standard* IFC used in the "sequential" technic, the mean uptake was 26.2%± 2.5% and for 300 μg of the *standard* IFC used in the "simultaneous" technic, the mean uptake was 19.0%± 2%. These values were based on 8 experiments for the "sequential" technic and 21 for the "simultaneous" technic.

The rank order of potency for the seven IFC's tested was the same with the "simultaneous" technic as with the Schilling test (Table 2). The "sequential" technic did not yield the same results. The possibility that the two *in vitro* methods measure only the binding ability of proteins in IFC for vitamin B_{12} was considered. Lysozyme, a substance known to bind vitamin B_{12}, but incapable of enhancing its absorption in PA patients (11) was used in the *in vitro* procedure with and without the addition of IFC. The results showed that lysozyme (300 γ) would lower the vitamin B_{12} uptake by the liver homogenate. When lysozyme was added together with IFC, the effect of IFC was not inhibited.

DISCUSSION

The results of the present study appear to indicate that IFC may be suitably assayed by the "simultaneous" *in vitro* technic. The curves obtained by the "simultaneous" technic regularly show a peak value, while in the "sequential" technic, an increase of binding in a linear manner can be observed. The reason

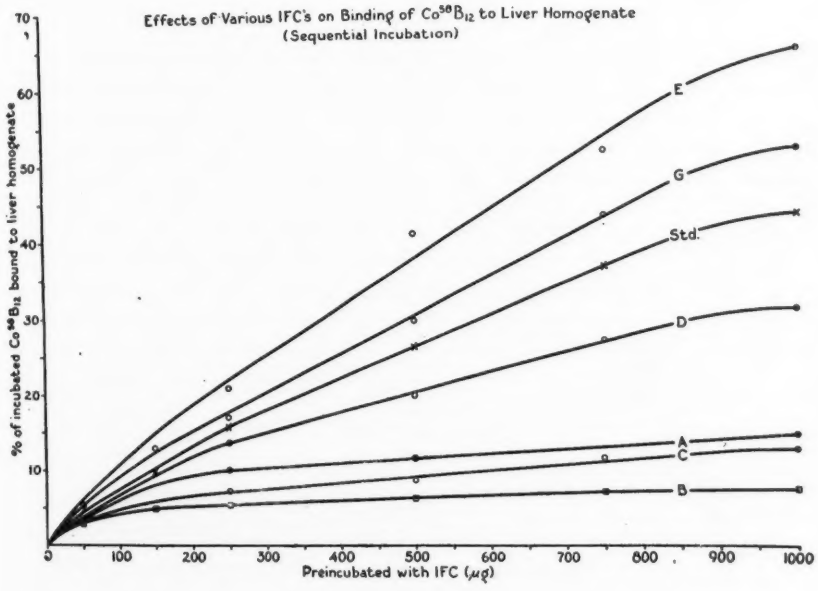

Fig. 1.

for this difference between the two types of curves may be attributed to the greater effectiveness of unidentified inhibitors present when IFC and vitamin B_{12} are "simultaneously" incubated. On the other hand when liver homogenate is pre-incubated with IFC and washed, the inhibiting substances or non-specific B_{12} binders may have been removed. In performing the Schilling test, such substances cannot be removed; therefore, a better correlation would be expected between the results of this test and the "simultaneous" technic than with the "sequential" technic. Herbert (19) did not advocate a "simultaneous" technic to be used for the purpose of assaying IFC because inhibitors and non-specific binding substances cannot be eliminated. However, since no IFC is free of such contaminates at the present time, it is believed that it is just this fact which contributes to the similarity of the results of the Schilling test with those of the "simultaneous" technic.

The reason for the variations in the magnitude of the peak values for vitamin B_{12} binding among the tested IFC's is not known. Minard and Wagner (17) also observed this variation. This may be attributable to the methods of purifying the IFC's. The three IFC's A, B, C were prepared from the standard IFC by column chromatograpy, and the remaining four IFC's were prepared by an extraction method. It is of interest that the chromatographically prepared IFC's showed peak values of Co^{58}-B_{12} binding by liver homogenate which were con-

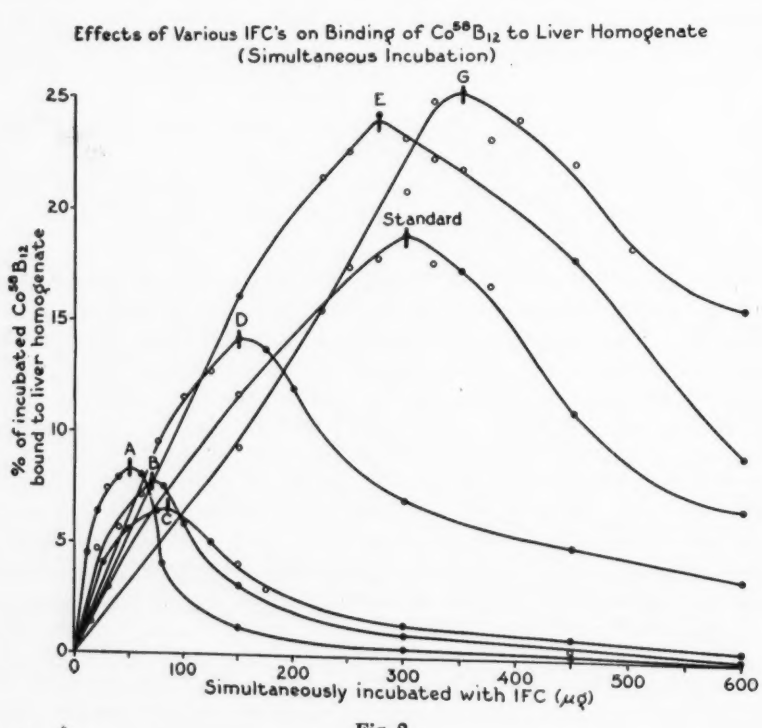

Fig. 2.

siderably lower than the peak values observed with the four remaining IFC's. Nevertheless, the magnitude of the peak levels did not correlate with the results of the Schilling tests while such a correlation existed when the concentration at which particular peaks occurred was considered. The lower this concentration the more effective was the IFC in the Schilling test.

The curves depicting the dosage-binding relationship in the "sequential" technic did not show the early peak, but conformed to linearity between the levels of 150 to 750 μg of IFC. When the slopes of these curves were considered a measure of the potency of the IFC's no correlation was apparent with their effectiveness *in vivo*. Actually, the most potent IFC's in the modified Schilling test resulted in the poorest response in the "sequential" technic. These results are at variance with those of Herbert (18, 19) who found "close relative correlation" of the "sequential" technic with the Schilling test. The reason for this discrepancy is not apparent. It seems improbable that differences in technic (Herbert used liver slices, Tris buffer and a different source of IFC) could account for it. Herbert has determined the relative potencies of the IFC's by the "sequential" technic only at one dose level while in this study the slope of the curve, established at varying dose levels, was used.

The flattening of the curves (Fig. 1) appears to suggest a "saturation" state for IFC binding by the liver homogenate. If the point of "saturation" had been adequately determined for each curve by using smaller increments of the IFC concentration, it is possible that a closer correlation between physiologic effectiveness and *in vitro* effectiveness of the "sequential" technic would have resulted. Further experiments are necessary for the elucidation of this question.

SUMMARY

Evidence has been presented in support of the feasibility of a "simultaneous" *in vitro* assay procedure for intrinsic factor concentrates. This procedure, consisting of the incubation of Co^{58}-B_{12} and intrinsic factor concentrates together with rat liver homogenate, has been shown to yield a potency-rank order for seven intrinsic factor concentrates which is the same as that found by a modified Schilling test. The "sequential" technic of pre-incubation of intrinsic factor concentrate in liver homogenate prior to the addition of Co^{58}-B_{12} could not be correlated with the results of the modified Schilling test.

It is suggested that the "simultaneous" assay method be used only as a screening procedure. The intrinsic factor concentrates, found to be effective *in vitro*, must continue to be tested in man until the isolation and purification of intrinsic factor has been accomplished.

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Abstracts of Papers Presented at the Second Annual Meeting of the Society of Nuclear Medicine, Southeastern Chapter, Atlanta, March 10-11, 1961

1. ***The Labelling of Proteins with Radioactive Iodine Utilizing Jet Iodination.*** **ALBERT J. GILSON (Department of Radiology, University of Miami School of Medicine, Miami).**

Selected lipid and protein substances can, under controlled conditions, be labelled with radioactive iodine. A series of relatively uncomplicated chemical techniques are involved in the actual iodinating process.

An iodination apparatus, based on the principles set forth by McFarlane, has been constructed and used in jet iodination of proteins. This method of iodination provides an efficient, rapid method for tagging small quantities of protein material.

2. ***Effect of Cortisone on a Diagnostic Test Employing a Sulfur-35 Organic Compound.*** **DANUTA MALEJKA, MARY ARGUS, AND F. E. RAY (Cancer Research Laboratory, University of Florida, Gainesville).**

Fluorene-2, 7-di-(sulfonamido-2′-naphthalene)-sulfur-35 is taken up by the spleen and liver of animals bearing tumors (*Brit. J. Cancer*, 10:321, 1956). If this is specific for neoplasia it might prove useful in the diagnosis of cancer. If the effect is a general stress phenomenon its value is questionable. Radiation did not produce this effect (*Proc. Soc. Exper. Biol. Med.*, 103:87, 1960). In the present investigation we tried the effect of chemical stress using cortisone as the agent.

Twenty-four (12m, 12f) 8-week old Wistar rats and 42 (18m, 24f) 7-week old CAF/Jax mice were used. Six male and 6 female rats, and 12 male and 12 female mice were given 4 subcutaneous injections of cortisone; 6 mg/rat, 3 mg/mouse/dose. The remaining animals served as controls. Twenty-four hours after the last injection of cortisone, 11.7 mg of a suspension of fluorene-2, 7-di-(sulfonamido-2′-naphthalene)-S-35 was given *via* the tail vein. Six hours later the animals were sacrificed. Cortisone treatment resulted in reduction of weight of spleen and thymus, but some effect of sex was found in the spleen. No significant difference in the uptake by liver and spleen of the radioactive substance was observed. This shows that stress created by cortisone is not similar to that of tumors in this system.

3. ***A Rapid Method for Measuring Labeled Protein and Other Materials.*** **RUSTY J. MANS (Biology Division, Oak Ridge National Laboratory, Oak Ridge).**

A method has been developed whereby proteins labeled with C^{14} and H^3 can be counted rapidly with a high level of precision and sensitivity. The method entails acid precipitating the labeled protein into a filter paper disk. Several disks are carried, batchwise, through a series of extractions and washings to remove nonprotein material. The ether dried disks are then counted directly in a liquid scintillation spectrometer. The counts detected by this method vary linearly with the amount of radioactive protein on the disk and are independent of sample volume and protein concentration over a wide range. Counting rates that are twice background can be detected accurately. Counting efficiency of C^{14} labeled proteins is 55% and of H^3 labeled proteins is of the order of 8 to 10%. The method can be adapted to measurement of materials other than protein and of isotopes other than C^{14} and H^3.

4. *Mathematical Correlation of Biological Data Using an Electronic Digital Computer.* JOHN U. HIDALGO (Tulane University, New Orleans).

A method has been described for the establishment of a prediction formula for blood volume in the normal human adult based on sex, height, and weight as the physical parameters.

The method uses the digital computer to perform the successive approximations necessary to establish the prediction formula. This is accomplished by supplying a test polynomial including the desired parameters (height and weight) and letting the computer establish the best coefficients of the polynomial to match the measured data (observed blood volume) with the computed data (predicted blood volume).

5. *An Analysis of the Effect of Apertures in Rotational Counting of Heterogeneous Radioactive Sources.* R. H. ROHRER (Veterans Administration Hospital and Emory University, Atlanta).

A system for measuring the activity of heterogeneously distributed radioactive materials that utilizes rotation of the sample and a unique aperture has been described by Dratz and Coberly. Experimental data obtained by these workers have shown that the aperture, when properly adjusted, may compensate for inverse-square law and self-absorption errors encountered in sample rotation counting. This allows one to use short sample-to-counter distances so that the efficiency of the counting geometry may be significantly improved without introducing serious errors due to nonhomogeniety of the sample. An analysis of the dynamic counting geometry showing the effectiveness of the aperture feature may be made with a simple model in polar coordinates. It is apparent that the aperture allows the detector to "see" radiation from a source located in the sample off the axis of rotation for a period that is less than the period of the rotation.

6. *The Use of Radioactive Triolein in Quantitative Studies of Intestinal Absorption.* JULIUS WENGER, JAMES C. COBERLY, AND ARTHUR F. DRATZ (Medical Service and Radioisotope Service, Veterans Administration Hospital, Atlanta).

Methods for determination of fat absorption are now sufficiently refined that fine differences in absorptive rates may be detected. Diarrhea alone will alter the rate of intestinal absorption of radioactive fat. Using each patient as his own control, a comparison was made with and without a saline laxative, and the preliminary results indicate that rapid motility through the upper small intestine tends to decrease the quantity of radioactive fat absorbed. This confirms a clinical impression that has been propounded in the literature, but not documented.

7. *The Use of Radioactive Intravenous Fat to Determine the Status of Liver Function.* J. R. MCLAREN, J. T. GALAMBOS, AND W. D. DREW (Department of Radiology, Grady Memorial Hospital, Atlanta).

A total of 27 patients was categorized as having normal or abnormal liver function on the basis of clinical and conventional laboratory data. This evidence was sufficiently conclusive to classify 11 patients as abnormal and 10 as normal. Of the remaining patients the information was either inadequate or conflicting.

After the intravenous injection of 2 ml of the fat emulsion, a 2-hour blood sample, 4-and 24-hour urine samples, and a tracing of the hepatic uptake for the first 30 minutes were obtained. These tracings were analyzed by the method of Lowenstein and the excretion and uptake half times were determined. Calculations were made of the percentage of injected radioactivity present in 1 liter of plasma after 2 hours, and the radioactivity excreted in 4-and 24-hour urine collections. These various determinations were analyzed by means of the Rank-Sum test, and significant differences were noted between the two patient groups for all the studies except the uptake half time.

8. *Calcium-45 Kinetics in Paget's Disease of Bone.* **Richard Goldsmith, and Mildred J. Wiester (Veterans Administration Hospital, Cincinnati).**

Eight patients with Paget's disease of bone were studied. Four demonstrated severe, widespread involvement of the skeleton; two demonstrated moderate and two minimal involvement. It was hoped that some generalization could be made that might help clarify this poorly understood clinical entity.

The data show that there is a direct relationship between the size of the eventual pool of radiocalcium distribution and the severity of the skeletal involvement. Furthermore, there appears to be a relationship between the value of the constant representing the fractional rate of change of pool size and the severity of the disease. The results of studies performed on the "control" subjects suggest that immobilization produces changes in bone formation kinetics similar to those found in Paget's disease.

The effect of therapy with adrenocortical steroids of the carbohydrate active series was also examined. These drugs produced changes in the parameters measured in the direction of normality. The same treatment produced changes of these parameters in the direction of abnormality in the one control subject so studied. It appears that Paget's disease is associated with some metabolic derangement that is present irrespective of the degree of skeletal involvement.

9. *Concomitant Radioisotopic and Radiographic Cerebral Arteriography.* **James Jackson, Barnes Woodhall, George Baylin, Ronald Krueger, and Aaron P. Sanders (Departments of Neurosurgery and Radiology, Duke University Medical Center, Durham, North Carolina).**

A group of neurological patients in whom tumors, hemorrhage or strokes were suspected comprised the study group. The common carotid artery of the neck was punctured percutaneously using local anesthesia. The usual placement of the needle was antegrade. Sometimes it was placed retrograde on the right side to obtain vertebral filling.

The contrast medium used was 50% hypaque (8 ml per injection). Conventional lateral and AP stereo roentgenograms were obtained. Between the lateral and AP arteriograms a radioisotopic study of the circulation pattern was made.

Twenty microcuries of iodine-131-labeled Hippuran in a 0.25 ml volume was manually injected into one orifice of a 3 way stopcock and immediately followed by an 8 ml injection of isotonic saline through the third orifice.

The collimated scintillation detectors were directed into the vertex of the skull. Each detector was collimated to "see" only one half the cranium. The output of each detector was fed to a count-rate meter and then to a rectilinear strip-chart recorder.

10. *An Aural Method of Analyzing Scan Records.* **C. C. Harris, P. R. Bell, and J. E. Francis (Oak Ridge National Laboratory, Oak Ridge).**

A novel use of a transistorized aural counting rate indicator shows promise in the process of analyzing scan records. Scan records made with dot tappers and digital photoscans are useful in that the recorded information can be unprejudiced. However, the area over which the eye integrates information tends to be fixed, and is a function of the recording method.

This new device allows one to choose an optimum integration area, and provides a method of analysis which does not alter the original data.

A light-sensing device (a silicon solar cell) is coupled to an aural counting rate indicator (howler) so that the frequency of a tone can be varied over a wide range in response to variations in light striking the light-sensor. This device, with a selection of apertures that define the area seen by the sensor, has been used to examine certain scan records. The records are placed on a light box, and the sensor used to "read" variations in density.

Preliminary investigation indicates that, with this method, the "ear can hear" information that is missed by the eye. Since the frequency range of the howler is from zero to about 15,000 cycles, and since zero frequency can be set at any chosen light level, the device is extremely sensitive to small changes in light transmitted through the record.

Analysis of scan records by this method has been made automatic. The light sensor, viewing through selected apertures, has controlled the printing of new, interpretive records.

11. *Medical Applications of the Personal Radiation Monitor.* R. H. Dilworth and C. J. Borkowski (Oak Ridge National Laboratory, Oak Ridge).

The Personal Radiation Monitor is a fountain-pen-sized radiation detection device providing immediate visual and aural indication of gamma or x-ray dose rate. Weighing only 3½ ounces, the self-contained instrument may be worn in the pocket to warn of entry into an unexpected radiation level, or it may be used as a probe to determine the extent of shielding or collimation of a known radiation source. Indications are given by flashing rate of a small neon lamp and the pitch of an audible tone, both of which increase in proportion to dose rate. The dynamic range of indication extends from background to 2 r/hr in the normal mode of use, and it is possible to fit the instrument with an attitude switch for range change that extends the upper limit of proportional indication to 200 r/hr merely by inverting the instrument.

The instrument operates continuously for one month in background from a 4-volt mercury battery. A 3-transistor circuit generates 500 volts for operation of a minature Geiger counter detector. A hearing aid earphone with a resonant air column provides the source of audible alarm tone.

12. *Intra-Arterial Yttrium-90 to Treat Cancer.* Edgar D. Grady, Walter Sale, and Luther Rollins (Departments of Radiology and Surgery, Piedmont Hospital, Atlanta).

Effective radiation must be concentrated primarily in the area of a cancer. To concentrate radioactive yttrium into an organ, we have used a particle made slightly larger than the capillaries. When such particles are injected into an artery, they stick in the tissue supplied by that artery.

Twenty-six rabbits have had arterial injections of suspensions of yttrium-90 made to specific size. Femoral artery, renal artery, carotid artery and portal vein have been injected. Animal experiments demonstrate that intra-arterial injection is an effective way of concentrating the isotopes into a specific organ. There is apparently no mechanical damage from the injections, the spill-over into the general circulation produces no obvious sequellae, and the radiation effect is homogeneous in the area treated.

13. *Effect of Total Body Irradiation on CNS and Blood Lipids of Rats.* Fred Snyder and Edgar A. Cress (Medical Division, Oak Ridge Institute of Nuclear Studies, Oak Ridge).

Small animals exposed to total-body gamma irradiation (TBI) show an elevated level of neutral lipids in the blood and a decrease in the biosynthesis of lipids in brain slices. Rats were given a total gamma dose of 840 r (70 r/min from cesium-137) and sacrificed 24 hours later. Gas chromatography was used to analyze the fatty acids of brain, plasma, liver, and adipose tissue of control and irradiated female CFN rats.

14. *Thyroid Function and Hepatic Injury by Cerium.* GRANVIL C. KYKER, JOHN RAFTER, AND FRED SNYDER (Medical Division, Oak Ridge Institute of Nuclear Studies, Oak Ridge).

An acute but transient hepatic injury is caused by cerium and other lanthanons. Specific metabolic knowledge is meager for these and other nuclear minerals, which offer both potential medical application and hazard. Fatty infiltration prominently reflects the metabolic upset and a broad scope of factors modify or prevent it. Among these, endocrine disturbances are especially noticeable including orchectomy, hypophysectomy, adrenalectomy, and alloxan diabetes. We are now reporting the effect of thyroid function on liver lipids after intravenous cerium (2 mg Ce per kg, as chloride) in rats (young adult, CFN, female). Normal and thyroidectomized rats, prepared surgically and by radioiodine, were compared. Basal metabolic rate and external scanning served to evaluate the prepared animals. Loss of thyroid function prevented the increase in liver lipids caused by cerium. Related considerations of energy metabolism prompted measurements that suggest a large intake of carbohydrate also to be protective. This additional scope to factors that modify or prevent rare-earth fatty liver extends the metabolic involvement of nuclear minerals.

15. *Radiation Nephritis; Review and Animal Study.* BRYAN L. REDD, JR. (Emory University, Atlanta).

The kidney has been long considered to be relatively insensitive to irradiation, even though isolated animal experimentation has demonstrated renal damage following X-irradiation. The occurrence of renal damage in man was reported as early as 1927. Awareness of this hazard has been renewed by articles published by Patterson and Kunkler, Farr, and Luxton. These authors report evidence of renal damage developing in approximately one fourth of those persons receiving radiation in excess of 2300 r in five weeks or less when both kidneys are in the irradiated area.

16. *Blood and Whole-Body Counts Following Neutron Irradiation in Man.* D. A. Ross (Medical Division, Oak Ridge Institute of Nuclear Studies, Oak Ridge).

After a person has received an accidental neutron exposure, it is customary to estimate, in retrospect, the magnitude of the dose received by calculations based on measurements of the induced activity in the patient's body, or in samples of blood withdrawn from it. It has generally been assumed that neutron-induced activity in normal human tissue is practically all due to the transformation of stable sodium-23 into radioactive sodium-24. This presentation is a brief, consideration of the extent to which the foregoing assumption is likely to be true, and on the other hand, of the extent to which other elements may obscure the picture. Potential complications will depend heavily on the counting procedure selected.

17. *The Proposed Adaptation of an Iridium-192 Industrial Radiographic Unit for Use in Interorificial Therapy.* ENOCH CALLOWAY (West Georgia Cancer Clinic Inc. of City-County Hospital, LaGrange, Georgia).

The original apparatus is a Picker Technical Operations Isotope equipment in which the source capsule is fixed to the end of a steel cable 50 inches long. This control cable passes over a crank driven wheel in the control unit, which advances or retracts the source from or into a safe lead pig. There is a system of positive signal lights. The cable works in a plastic covered flexible steel guide tube.

The end of this tube has been narrowed and lengthened to fit into and is secured to a master cone or speculum 10 cm long. Various sizes and shapes of cones may be interchanged and attached to the end of the master cone. These cones have a minimum of 3 half value layers of protection.

By changing the size, shape, and angles of the interchangeable end cones a great facility in treatment can be obtained.

Although at present we are chiefly interested in iridium-192, sources may be easily and safely changed and other sources may be used.

18. *Cobalt-60 Leaks in Teletherapy Units.* MARSHALL BRUCER (Medical Division, Oak Ridge Institute of Nuclear Studies, Oak Ridge).

On September 8, 1958, a teletherapy technician approached a scanning device on which a patient was being scanned. As he neared the machine, the scanner recorded counts that were obviously not from the patient. Upon checking with smear tests it was found that he had been contaminated with a small amount of cobalt-60. Activity was insufficient for any personnel danger, but was sufficient to allow smear tests to record the contamination throughout the Medical Division and in the personal property of the technician.

Before decontamination the smear tests indicated appreciable fractions of one microcurie of cobalt-60 throughout the Medical Division. About 15 microcuries were found in the throat of the collimator of the machine in which the activity was released. After routine decontamination procedures, the activities were reduced to less than 0.01 microcurie throughout the area.

A conference of maufacturers of teletherapy equipment was held on December 1, 1958, during which a new encapsulation technique was adopted. Since this meeting a little more than 10 per cent of all the old sources have been known to leak powdered cobalt. No source of cesium has yet been known to leak, and no source of cobalt in the new encapsulation has been known to leak. A method for the rapid detection of leaks has been proposed.

19. *On the Mechanism of Action of Thyrotropin on the Thyroid.* J. A. PITTMAN, D. HAMNER, AND B. H. WILLIAMS (Veterans Administration Hospital and University of Alabama Medical Center, Birmingham).

Thyrotropin (TSH) not only accelerates the rates of various steps in thyroid hormone formation and release, but also those of oxidation of D-glucose-1-or-6-C^{14} to $C^{14}O_2$. Incubation of fresh beef thyroid slices in 2 ml of a medium of phosphate buffer containing 0.03 mg of pyruvate and 0.5 microcurie of sodium pyruvate-2-C^{14} led to the evolution of $C^{14}O_2$, which was trapped in hyamine and counted in a liquid scintillation counter. Oxidation of the labeled pyruvate was enchanced by the addition of TSH (1.0 unit/flask). This enhancement by TSH still occurred in the presence of 10^{-6} M fluoride, and was only slightly less at 10^{-5} and 10^{-4} M fluoride. Thus, TSH would appear to be acting on the tricarboxylic acid cycle side of enolase.

Formation of a sulfur-sulfur bond in the hormone-receptor interaction has recently been proposed as the mechanism of action of vasopressin on the kidney (Fong *et al.*, Rasmussen *et al.*, and Schwartz *et al.*, Proc. Nat. Acad. Sci., Oct., 1960). Vasopressin can also stimulate release of thyroidal PBI^{131} (Lipscomb *et al.*, Clin. Research, Jan., 1961), and cysteine is the most abundant amino acid in TSH (Pierce *et al.*, Ann. N. Y. Acad. Sci., April 23, 1960). These data, with others, suggest that TSH may alter thyroid cellular permeability to several substances and that this change may be mediated by a thiol-disulfide exchange reaction similar to that proposed for vasopressin.

20. *Suppression of Thyroidal I^{132} Uptake by Various Medications.* E. F. McCraw and J. A. Pittman (Veterans Administration Hospital and University of Alabama Medical Center, Birmingham).

The thyroidal I^{132} uptakes in 20 minutes (using a subtracting circuit to correct for non-thyroidal neck counts and plotting the resultant curve on a chart recorder or subtracting thigh count from neck count at 20 minutes) have been determined in 158 patients after administration of 2 to 5 μc of the NH_4I^{132} intravenously. None of the eleven hyperthyroids had an uptake of less than 18% (mean = 37; range = 18 to 77%); euthyroids had a range of 1.5 to 8.0%, with a mean of 5.4%. All of the three hypothyroids had values below 1.5% (mean 0.4%; range = 0 to 1.5%).

After three baseline determinations had been obtained in six euthyroids, they were given either 750 or 375 micrograms of L-triiodothyronine (T3) orally in a single dose and the rate of suppression and recovery of I^{132} uptake followed by serial determinations. In all but one suppression was evident at six hours and this was maximal at ten hours after the dose. At 28 hours normal values had again been reached. No difference has been found between the two doses thus far. Similar studies with five patients given single 750 microgram oral doses of sodium L-thyroxine (T4) showed suppression in all patients within six hours after the dose. The suppression lasted for approximately five days with a more gradual recovery thereafter. The suppression six hours after T3 was only moderate (about half the baseline value). Six hours after T4 the uptake was suppressed to about 1% or less in all patients, and this value approximated the maximum suppression in these patients. The molar ratio of the dose of T4 to the larger dose of T3 is 0.84. Thus, the ratio of T3 to T4 activity is different in this situation from the common value of about 4.

21. *Analysis of the Radioactive Renogram Curve by an In Vitro Experiment.* Felix J. Pircher, Audrey W. Wegst, and Vernon N. Dodson (Department of Radiology, University Medical Center, Indianapolis).

Radioactive renography uses scintillation detectors to record the rate of tubular secretion of an iodinated contrast medium independently for each kidney. The technique produces a curve in which every point represents count rate versus time; it is characteristic only for renal activity. The "normal" curve is defined by half time of count rate increase, half time of count-rate decrease, the maximum count, and the time at which the maximum count occurs. Theoretical considerations have led us to construct a model that simulates the physiological situation in a radioactive renogram test and consists of two compartments between which a radioisotope dilution was exchanged. Several experimental runs varied: (1) the flow rate; (2) the volume of compartment one; (3) the volume of compartment two. The activity was constant (25 microcuries of iodine-131). The results indicate that the flow rate, the kidney volume, and a fraction of the blood volume are the factors that determine the renogram curve.

22. *Tubular Loading as a Means of Improving the Radiorenogram.* William DeMaria, Ronald Krueger, Aaron Sanders and George Baylin (Departments of Pediatrics and Radiology, Duke University School of Medicine, Durham, North Carolina).

Concentration and secretion of the iodine-131 Hippuran dose used in the standard renogram requires little renal function and thus may appear normal even when significant renal disease exists. We have demonstrated this to be true in dogs with unilateral renal dysfunction. This deficiency was easily noted if the tubular mechanism responsible for removal of the iodine-131 Hippuran was first saturated with a competing substance, paraamino-hippurate (PAH). As the blood level of PAH falls, repeat renograms at about 15 to 20 minute intervals reveal both an earlier and greater concentration and secretion of iodine-131 Hippuran by the normal kidney.

This technique has been applied to human controls as follows:

A routine renogram is performed using iodine-131 Hippuran. Fifty milliliters of 20% PAH is then injected intravenously in 5 to 7 minutes. The renogram is repeated immediately upon completion of the PAH injection (No. 1) and again 20 (No. 2), and 40 (No. 3) minutes later.

The No. 1 renogram uniformly shows minimal to no concentration or secretion of iodine-131 Hippuran. About 90% show good concentration and secretion in the No. 2 renogram and essentially all show a return to the control pattern on the No. 3 renogram. Average levels of blood PAH during the No. 1 renogram is 75 mg per 100 ml, and is 35 mg per 100 ml and 17 mg per 100 ml during the No. 2 and No. 3 renograms.

23. *A Descriptive Analysis of Vascular Beds.* J. M. James, Allen M. Lesage, G. S. Eadie, and W. Glenn Young (Department of Radiology, Duke University Medical Center, Durham, North Carolina).

Surgical techniques for extracorporeal circulation are used to delay recirculation of a radioactive plasma label I^{131} by temporarily diverting the return flow from an organ or other region into a second reservoir and maintaining the circulation from a reservoir containing unlabeled blood. Detection is accomplished by passing the return flow through a glass coil surrounding a sodium iodide crystal, fed to a countrate meter then to an Esterline-Angus strip recorder. The record, 2 to 3 minutes long, can be regarded as a frequency diagram of pathway times between the point of injection and that of observation.

As an example of studies made possible by this technique, curves have been made of the systemic flow in dogs at normal body temperature and at 10°C. At normal temperatures the curve consists of an initial peak of fairly constant form followed by a variable plateau. At low temperatures the initial peak is delayed and is followed by a smooth fall resembling an exponential curve.

Announcement

A five-day course entitled "Advances in Clinical Radioisotope Instrumentation" will be offered October 23-27, 1961, at the Medical Division of the Oak Ridge Institute of Nuclear Studies. It is designed for physicians and paramedical personnel who already have experience in handling radioisotopes. Limited to forty participants, the course will consist of lectures and demonstrations and will cover theory and practical aspects of liquid, crystal, and gas detectors. It will include topics on circuitry, electronics, data processing, scanning, dosimetry, and calibration. There are a few vacancies remaining in the course. Application forms are available from Ralph M. Kniseley, M.D., Medical Division, Oak Ridge Institute of Nuclear Studies, Post Office Box 117, Oak Ridge, Tennessee.

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Annual Meeting Report

The Society of Nuclear Medicine recently concluded its 8th Annual Meeting at the Penn-Sheraton Hotel, Pittsburgh, Pennsylvania. A record attendance of over 500 physicians and other scientists from the United States of America and other countries were in attendance and over 80 scientific papers were presented.

Prof. George C. de Hevesy of the University of Stockholm, Sweden, winner of the 1943 Nobel Prize in Chemistry and the Second Atoms for Peace Award in 1959, presented the second of the Annual Lecture Series—a series of lectures dedicated to pioneers in nuclear medicine—in honor of Marie and Pierre Curie, and Henri Becquerel. At this meeting Prof. de Hevesy received his Honorary Membership certificate from The Society of Nuclear Medicine.

The following officers were elected to serve from June 16, 1961 through June 29, 1962:

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In addition, the following were elected as members of the Board of Trustees for a term of three years:

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The Executive Committee approved 191 applications for membership in the Society bring the total membership to 1,738. The Publication Committee announced that effective January 1962, the Journal of Nuclear Medicine will be published on a bi-monthly basis instead of quarterly. There will be no increase in dues and the non-member annual subscription price will remain at $10.00 for 1962. The 9th Annual Meeting of the Society will be held at the Baker Hotel, Dallas, Texas, June 27-30, 1962. Dr. Herbert C. Allen, Jr. of Houston, Texas will serve as the Chairman of the General Arrangements Committee and Dr. Donalee Tabern of Chicago, Illinois has been appointed the Chairman of the Scientific Program Committee.

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Radiopulmonography: A Simple Method For Simultaneous Estimation of Individual Lung Function.[1]

MAURICE J. SMALL, M.D., WADE N. MILLER, M.D., GEORGE C. LEINER, M.D., HERBERT D. STRAUSS, A.B. AND SOL ABRAMOWITZ, B.S.

PRELIMINARY NOTE[2]

In recent years, isotopic and electronic methods have been devised for the estimation of individual lung function without resorting to bronchospirometry (1-4). These methods employing either labelled inert gases (1), complex laboratory assembled electronic gear such as photomultiplier tubes for measuring light emitted by a crystal which is excited by passage of fairly heavy x-ray dosage through the lungs (2,3) or x-ray sensitive cadmium cells (4) do not readily lend themselves to routine clinical use. Details of instrumentation used in these procedures are not published, so that attempts to verify these methods are most difficult.

The methods employing labeled inert gases depend for their validity on the concentration of gases remaining in an area of lung at any given time. The method here presented utilizes the passage of low voltage x-ray through the chest and measures the exit beam. Respiration alters the linear density of the lung tissue and thereby alters the intensity of the exit beam. Inspiration decreases the linear density and increases the exit dose while expiration increases the linear density and decreases the exit dose. These intensity changes, recorded over time, result in characteristic curves which are distorted in the presence of pulmonary disease.

Radiopulmonography utilizes readily available commercial apparatus. The source of radiation is an inexpensive portable x-ray machine, and the detecting apparatus is a dual scintillation detection system consisting of 2 matched probes, dual ratemeters and a dual recorder, equipment available in most clinical radioisotope laboratories.

Routinely, the subject is seated with the x-ray source 6 feet from the anterior chest wall. The dual probes are placed on the posterior chest wall in contact with the skin. Separate recordings are made over the upper, mid, and lower lung fields. Identical recordings have been obtained if the patient is rotated 180 degrees and the x-ray beam enters posteriorly and is measured on the anterior wall.

The x-ray source operating at about 25 KV and less than 0.5 ma is beamed at the patient. Recordings are made with a ratemeter time constant of 0.5 sec-

[1]From the Radioisotope and Cardiopulmonary Laboratories, Veterans Administration Hospital, East Orange, N.J.

[2]See page 252.

onds, using the 300 K scale, and a paper speed of 6 inches per minute. The total time required for the examination is 10-15 minutes and the radiation received by the subjects has been measured at less than 5 milliroentgents for the entire procedure.

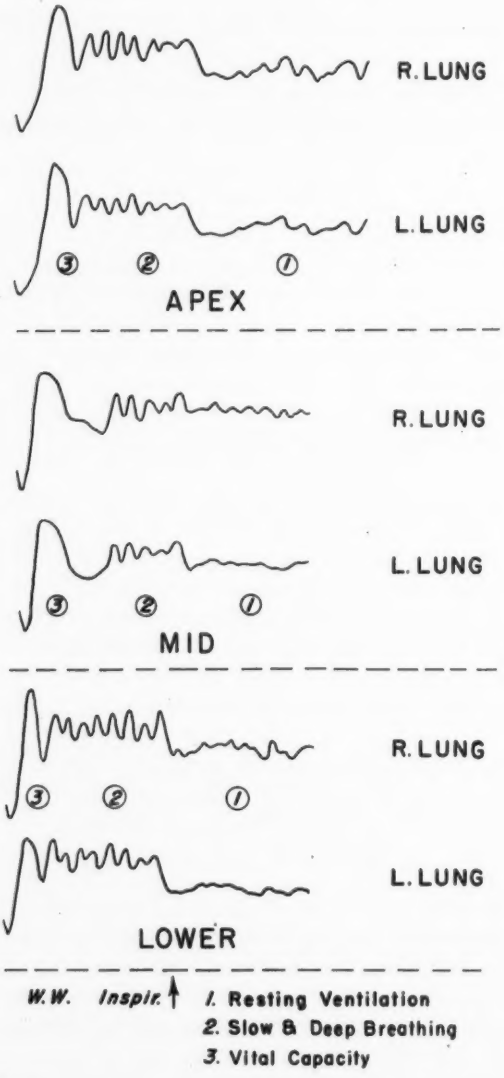

Fig. 1. Normal Tracings

Figure 1 illustrates a normal tracing. It shows resting ventilation, slow and deep breathing, and vital capacity over the apical, mid and lower portions of

the lungs. Characteristically, the amplitude of the deflections, which can best be appreciated during slow and deep breathing, increases as one progresses from the apical to the basal portion of the lung field with the exception of the left lower lung, where the presence of the heart probably accounts for the decreased excursions on the left as compared to the right.

In addition to normal individuals, patients with a large variety of pulmonary diseases are being studied by this method; These include patients with emphysema, lung tumors, pulmonary infections, infiltrative and cavitary tuberculosis, pleural effusions and thickened pleura, and patients before and after pulmonary surgery.

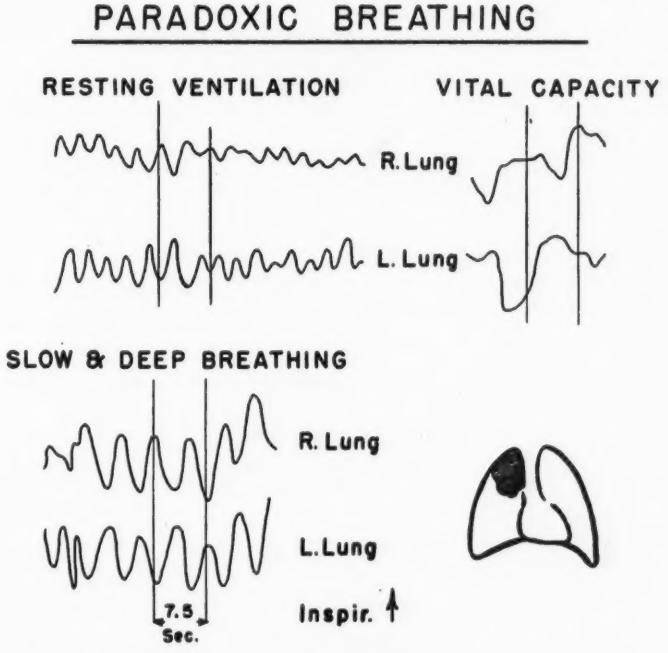

Fig. 2. Paradoxic Breathing

Through the use of radiopulmonography, it is possible to demonstrate graphically the phenomenon of paradoxic breathing, i.e. to show a localized breathing curve which is completely out of phase with that of the normally breathing lung. In order to determine which area is breathing paradoxically, we have made spirometric tracings at the mouth and over the lung fields. This is at present being done with another recorder that is electrically synchronized by marker signals with the dual lung tracings. The finding of paradoxic breathing has been seen by us in only two conditions, namely pulmonary emphysema and carcinoma of the lung. Figure 2 illustrates this finding in a hilar type of carcinoma showing a lesion extending from the right hilum into the right upper lobe. Long

stretches of paradoxic breathing may be noted here during resting ventilation, slow and deep breathing, and vital capacity.

In contrast to bronchospirometry, which has been used for many years to obtain information about individual lung function, this procedure is completely painless and harmless to the patient, and does not subject him to intubation. More important, this method permits study of small portions of the lung, whereas bronchospirometry estimates function of each lung as a whole. We are hopeful that further use of radiopulmonography may contribute to a better understanding of pulmonary pathophysiology and that with further refinements in technique and standardization, it might be possible to quantitatively estimate the physiological function of localized lung areas.

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Announcement to Authors
Preliminary Notes

Commencing with the October, 1961 issue, space will be reserved in each issue of THE JOURNAL OF NUCLEAR MEDICINE for the publication of one preliminary note concerning new original work that is an important contribution in Nuclear Medicine.

Selection of the preliminary note shall be on a competitive basis for each issue. One will be selected after careful screening and review by the Editors. Those not selected will be returned immediately to the authors without criticism. Authors may resubmit a rejected or revised preliminary note for consideration for publication in a later issue. The subject material of all rejected manuscripts will be considered confidential.

The text of the manuscript should not exceed 1200 words. Either two illustrations, two tables, or one illustration and one table will be permitted. An additional 400 words of text may be substituted if no tables or illustrations are required. Only the minimum number of references should be cited.

Manuscripts should be mailed to the Editor, Dr. George E. Thoma, St. Louis University Hospital, 1325 South Grand Blvd., St. Louis 4, Missouri. They must be received before the first day of the month preceding the publication month of the next issue, e.g., preliminary notes to be considered for the January issue must be in the hands of the Editor before December 1.

JOURNAL OF NUCLEAR MEDICINE 2:253-271, 1961

Neutron Capture Therapy of a Cerebellar Hemangiosarcoma After Surgical and Radiation Treatment[1,2]

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INTRODUCTION

Neutron capture therapy has been, since 1950, under continuing experimental exploration for the treatment of Glioblastoma multiforme at the Medical Research Center of Brookhaven National Laboratory. In this procedure thermal neutrons trigger a reaction with boron-10 atoms, which then almost instantaneously disintegrate and cause localized selective cytocidal effects. The immediate clinical responses and routine pathological study of a small number of these cases have been reported previously (1, 2, 3, 4, 4a).

1. From the Medical Research Center Brookhaven National Laboratory, Upton, L.I., New York.

2. This research was supported by the U.S. Atomic Energy Commission.

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In the present instance, the procedure was tested with a radically different type of tumor, sarcoma, of presumed vascular origin in a region of the central nervous system where absolute precision of destructive efforts must obtain in cancer control. This report also gives data on the effects of very extensive local thermal neutron exposure to the central nervous system—an exposure far in excess of any other documented data in the literature dealing with thermal neutrons. Furthermore, previous x-ray and surgical efforts had not brought the neoplasm under control. In addition, before neutron capture therapy, the patient showed a carbon dioxide plasma content far in excess of any previously recorded value we could find. For these reasons, the material is here presented before the definitive serial section study of the central nervous system can be completed.

The principle of the basic procedure used has been previously discussed in the literature (5). However, the dose delivered in this instance by the use of the new Medical Research Reactor significantly exceeded all previous quantitative observations. The fact that the major exposure occurred in the brain stem region, presumably a highly radiosensitive region, permits a meaningful comparison with other radiation procedures of this region and a better evaluation of some of the advantages of neutron capture therapy.

The patient was an eleven year old female, who had a past history of right retroauricular hemangioma (7 x 3 cm in size and 1 cm elevation) present at birth. For this she had received a total 315 r, 125 kyp x-ray therapy at the age of 3 months. The treated area was demarcated by depilation and depigmentation. The patient's growth and development were normal. No unusual childhood diseases are recorded. However, when the patient was 10 years old, at the end of October 1957, cyclic vomiting, anorexia and frontal headache developed. She was admitted to a hospital and carefully studied without development of any signs pointing to a specific neurological disorder. With remission the patient was discharged home. However, signs and symptoms promptly recurred necessitating readmission.

At that time after extensive study an intracranial lesion was suspected and on November 16, 1957, suboccipital craniectomy was performed by Dr. William German at the Grace New Haven Community Hospital, New Haven, Connecticut. A large soft white tumor was found on the lateral aspect of the right cerebellar hemisphere and the tumor was partially excised. Histological examination revealed a malignant vascular neoplasm in the cerebellum [Hemangiosarcoma by the classification of Cushing and Bailey (6), (Fig. 1)]. Post-operatively the surgical wound was infected with hemolytic staphylococcus aureus. On account of the infection and drainage, the patient was not referred for radiation therapy until January 21, 1958.

Between January 21, 1958 and February 28, 1958 the patient received 17 x-ray treatments through the left parietal region, 16 treatments through the right parietal region, and 4 treatments through the occipital region, directing to the cerebellum using 10 x 10 cm ports. The calculated maximum skin dose was 3986 r in the parietal region and the calculated tumor dose in the cerebellar region was 3499 r in 38 days. The physical factors used were: 250 kvp, composite filter, 50 cm target skin distance, and the half value layer of the radiation was 3 mm copper.

Because of the presence of multiple draining abscesses in the occipital region, the x-ray treatment could not be given to the highest possible level of tolerance, therefore, a series of additional treatments to the cerebellar regions was resumed between March 31, 1958 and April 16, 1958; four treatments through the right parieto occipital region, four treatments through the left parieto occipital region, three treatments through the occipital region, and three treaments through the vertex, all directed to the cerebellum, using 10 x 10 cm portal size were given. The calculated maximum skin dose at this time was 1192 r to the parieto-occipital region and the calculated tumor dose was 1510 r. The physical factors used were

similar to the previous one with the same 250 kvp machine. Between May 26, 1958 and June 26, 1958, seven treatments to the dorsal spine and eight treatments to the lumbo-sacral spine were given through 10 x 10 cm ports. The calculated tumor dose was 1440 r to the dorsal cord and 1464 r to the lumbo-sacral column in four weeks time. During above treatments, rather marked nausea and vomiting were noted and she remained stuporous. In addition progressive extension of tumor mass from the suboccipital area to the right posterior neck region was noted. Biopsy of this extending mass in the right posterior neck region showed this to be identical with the tumor previously found in the cerebellum.

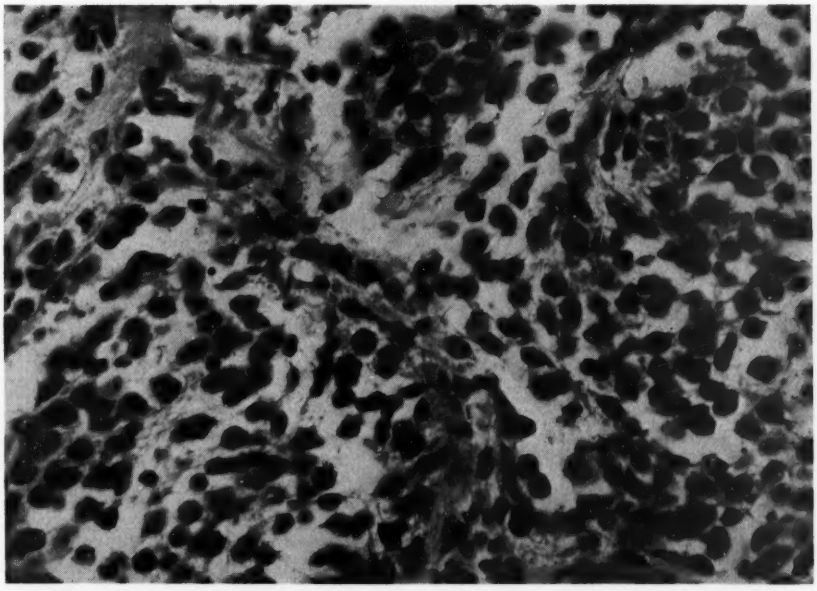

Fig. 1. Histology of neoplasm found at original operation. Classified as Hemangiosarcoma x 400.

Between July 23, 1958 and August 9, 1958, eight more x-ray treatments tangential to the right lateral cervical and eight treatments tangential to the left lateral cervical area were given through 6 x 8 cm ports. The calculated tumor dose was 2944 r in 17 days. The physical factors used were as before. Despite these treatments the patient remained drowsy, and became increasingly stuperous until deep coma supervened presumably from neoplastic expansion. Ultimately it was noted that the tumor had extended progressively from the suboccipital area to the right anterior area over the right sternocleidomastoid muscle to the angle of the mandible.

In late October 1958 the patient reached an obviously critical state with Cheyne-Stokes respiration, deep coma, and massive spasticity without voluntary movements in all extremities. Respiratory distress necessitated a tracheotomy

prior to removal to Brookhaven National Laboratory Medical Research Center. On admission (October 31, 1958), the patient was in a deep coma, and had unstable vital signs and Cheyne-Stokes respiration. The blood pressure fluctuated from 110 to 170 systolic, and 70 to 100 diastolic. Pulse was 60 to 150. Respiratory rate was depressed and rhythm was quite irregular so that tracheal tube and oxygen administration were required.

The palpable suboccipital mass on the right side of the suboccipital and neck regions was 12.7 x 15.3 cm in diameter. (Fig. 2 and 3). The tumor depth was estimated to be approximately 9 cm. There was cystic formation or cerebrospinal

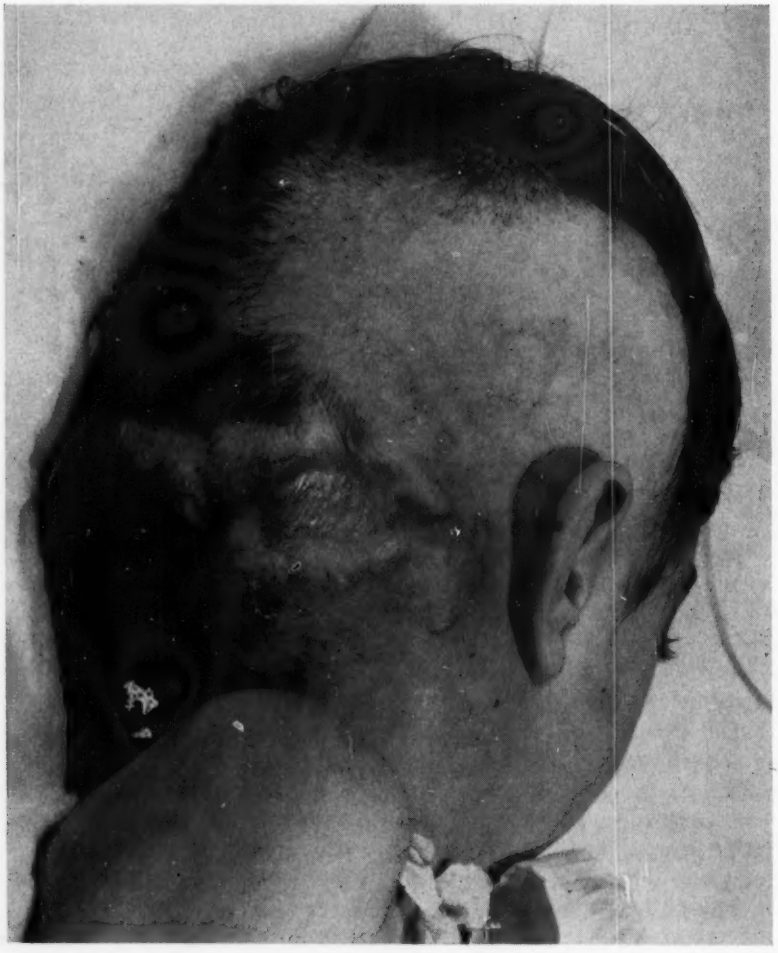

Fig. 2. Photograph of patient taken before neutron capture therapy showing subcutaneous and nodular extension of the neoplasm.

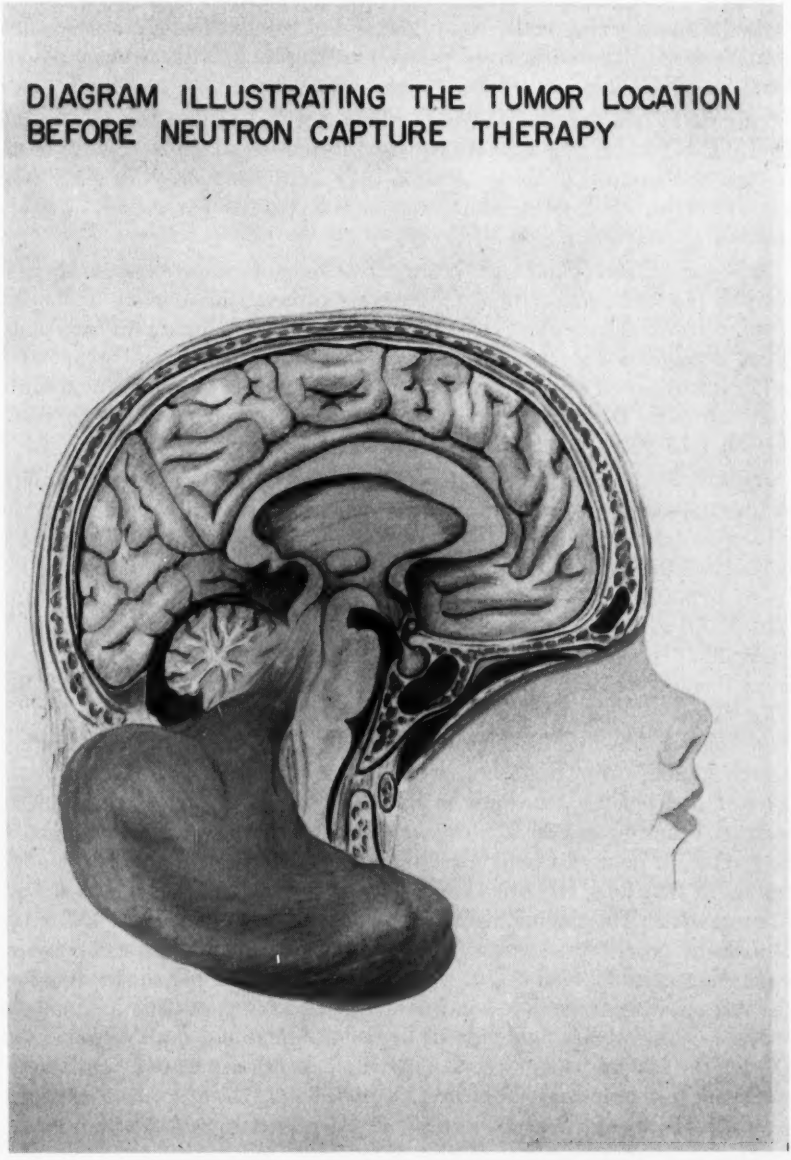

Fig. 3. Diagrammatic sketch of neoplasm in sagittal section before neutron capture therapy.

fluid in the left side of suboccipital area which was connected to the ventricular system. There was depilation of the bi-parieto-occipital area due to x-irradiation. Neurological examination showed normal optic discs and no evidence of hemangioma in the retina. The pupils were dilated and reacted to light slowly. There was marked spasticity with flexed position without voluntary movements on all extremities. There was marked ankle clonus bilaterally.

Laboratory studies on admission showed CO_2–35.34 mEg/L; Na–140.5 mEq/L; K–4.00 mEq/L; Cl–96.23 mEq/L; BUN–8.10 mg%; Ca–10.79 mg%; P–7.43mg.%; Protein–7.67 gm%; Albumin–3.88 gm%; Globulin–3.79 gm%; Hemoglobin–12.7%gm; Hematocrit 39.5%; and W.B.C.–10,700 per cu.mm. Urinalysis was within normal limits.

Suboccipital and spinal taps showed that communication between these two areas was blocked. Suboccipital taps were required almost every 12 hours to relieve pressure. The patient's respiration as well as neurological and general physical conditions became progressively worse after admission. Artificial respiration was required on the night of November 4, 1958. A suboccipital tap did not seem to alter the respiratory pattern. At this time, the blood CO_2 was increased to 56.5 mEg/L and the blood pH was 7.41.

Approximately 15 minutes after artificial respiration was begun, a massive tonic contraction of all extremities, opisthotonos, and trismus occurred. There were fine twitching of the left side of the face and the right leg. The right eye was fixed and the left eye deviated to the right. Because of the similarity of these signs to hypocalcemic tetany, 1.0 gm of calcium gluconate was given intravenously. All motor symptoms subsided immediately after this medication, and all extremities became flaccid. Despite the patient's desperate condition, neutron capture therapy was carried out on November 5, 1958. At that time 36.8 mg B^{10}/Kg (total of 1791 mg boron-10) as sodium pentaborate in 100 cc of 20% glucose solution was injected into the anticubital vein over a 10 minute interval. Although sodium pentaborate is less toxic than borax, it still causes respiratory depression and emesis. However, in this case there was no serious respiratory depression, vomiting, or E.K.G. change during and after boron administration. The patient received neutron irradiation 8 minutes after completion of boron administration. At that time, the Brookhaven Research Graphite reactor was operated at 16 megawatts. The thermal neutron flux at the skin entrance was 1.96×10^9 n per square centimeter per second. Exposure time was 20 minutes and 6 seconds. The patient received a total of 2.35×10^{12} thermal neutrons per square centimeter at the skin entrance through a 4 inch diameter circular port. The neutron cloud was directed toward the right side of the suboccipital and neck regions. Table I. During the first 24 hours after therapy the patient's respiration continued depressed with further increase in blood CO_2 to 64.9 mEg/L. (Fig. 4). Temperature was also markedly elevated to over 40° C. Her vital signs became normal on the second day after therapy. Within three days progressive softening of the tumor was clearly evident by palpation, and by measurement regression of the neoplasm on the right side of the suboccipital and neck regions could be demonstrated.

A biopsy of the tumor was performed two weeks after neutron capture therapy. The specimens were taken from within and without the neutron exposure field area. At that time it was noted that the exposed tumor was quite fluid and necrotic, but the non-irradiated tumor was still of the same solid consistency. A histological observation of this material has been reported (7). However, since the port employed was not designed to allow radiation to all of the neoplasm, an additional segment of the neoplasm in the suboccipital area was subjected to neutron capture therapy on January 22, 1959, eleven weeks after the first regional treatment.

Physical examination prior to the second treatment showed her still to be in coma with marked respiratory depression. This required the almost continual use of a respirator, though the patient could occasionally be taken out of the respirator for up to 3 hours. Neurological examination showed early papilledema, right facial weakness and a marked spasticity of all extremities, with hyperactive deep tendon reflexes and positive left wrist clonus. The right suboccipital mass measured 5.5 cm x 5 cm by palpation on the right side of her suboccipital area. The three superficial masses on the left side of the suboccipital area, which was well outside of the first irradiation area, had grown rapidly during the last three weeks and measured 5 x 5 cm, 2.5 cm x 2 cm, and 2 x 2 cm. Biopsy of these masses showed the same histological structure seen initially.

For the second treatment on January 22, 1959, 32 mg B^{10}/Kg (total of 670 mg boron -10) as sodium pentaborate with glucose was given into the right antecubital vein during a 9.5 minute interval. During the boron infusion respiration was quite depressed and required manual artificial respiration a few times. However, there was no nausea or vomiting during and after boron administration. The patient received the thermal neutron exposure in the Brookhaven Research Graphite Reactor 24 minutes and 43 seconds after boron administration.

At this time it was planned to expose the entire suboccipital area and upper part of the cervical region with a large trapezoid shaped port (4 x 5 x 6 inches). The Brookhaven Graphite Research Reactor was operated at a power of 16 megawatts during the period the shutter was open. The thermal neutron flux was 2.31×10^9 per square centimeter per second at the skin entrance. Exposure time was 25 minutes and 11 seconds. The patient received a total of 3.49×10^{12} thermal neutrons per square centimeter at the skin entrance, Table 1.

The patient had remarkable improvement in clinical status as well as further tumor regression after the second treatment. Eight days after therapy, the patient became conscious and tolerated being out of the respirator. Her blood CO_2 concentration became and remained normal. A mild horizontal nystagmus and edema of her face observed the second day after the second treatment disappeared within a week.

Fifteen days later, after four and one-half months of deep coma, the patient became fully conscious and talked without difficulty. Three weeks after therapy, the patient was up in a wheel chair, and showed a wide range of voluntary movements of all extremities. Her vital signs were stable, and there were no signs of respiratory depression at that time. The palpable tumor masses rapidly

Table I

Reactor and Date of Treatment	Boron-10 Dose		Interval Time from Boron Administration to Neutron Exposure	Thermal Neutron Exposure		
	mg/kg	Total Boron (gm.)		Neutron Flux $n/cm^2/sec.$	Exposure Time	Total $Neutrons/cm^2$
B. G. R. R. November5, 1958	36.8 I. V. (10 min.)	1.7913	8 min. 57 sec.	1.96×10^9	20 min. 6 sec.	2.35×10^{12}
B. G. R. R. January 22, 1959	31.94 I. V. (9.5 min.)	0.6707	20 min. 43 sec.	2.31×10^9	25 min.	3.46×10^{12}
B. G. R. R. April 13, 1959	36.0 I. V. (10 min.)	0.93	25 min.	1.61×10^9	25 min.	2.43×10^{12}
M. R. R. June 25, 1959	35.1 I. V. (5 min.)	1.1716	31 min.	2.36×10^{10}	204 sec.	4.81×10^{12}

Table I. Tabular summary of boron administration and dosage, delay interval and duration of neutron exposure with intensity B.G.R.R is Brookhaven Graphite Research Reactor MRR is Medical Research Reactor.

reduced in size after the second exposure. There remained only a small palpable mass, on the right suboccipital area. We could not establish this to be neoplasm. Other palpable masses had completely disappeared seven weeks after the second probe. On March 11, 1959 a biopsy was done on the right side of her suboccipital area. The specimen was removed from a depth of 4 to 5 cm in the formerly recurrent tumor mass area. This biopsy revealed only fibrous scar tissue. However, eleven weeks after the second treatment, the tumor mass on the right side of her suboccipital area had again enlarged to 8 x 7 cm in size. The patient became quite depressed and required tube feeding. Physical examination showed stable vital signs and normal respirations, but there was more spasticity of her right lower extremity with positive right ankle clonus. Positive upon neurological Babinski and Hoffman signs were present bilaterally.

On April 13, 1959 the patient received neutron capture therapy for the third time, eleven weeks after the second probe. At that time a dose of 36 mg. B^{10}/Kg (930 mg. total B-10) as sodium pentaborate with glucose was given in the right antecubital vein during a 10 minute infusion. There were no signs of boron toxicity during and after administration. The neutron exposure was given 25 minutes after boron administration in the Brookhaven Research Graphite Reactor, with the graphite reactor operating at a power of 16 megawatts. The thermal neutron flux at the skin entrance was 1.61×10^9 n per square centimeter per second. The entire suboccipital area was exposed for 25 minutes with 4 x 5 x 6 inch trapezoidal shaped port. The patient received a total of 2.43×10^{12} thermal neutrons per square centimeter at the skin entrance, Table 1.

Approximately five hours after treatment a quite remarkable edema was noted involving her entire face as well as the irradiated area. This edema disappeared within 6 days. Her vital signs were stable and there was no elevation of temperature after the treatment. The patient became conscious, and started vocal conversation six days after the third treatment. Complete depilation, pigmentation, and superficial ulceration developed on the entire irradiated area approximately two weeks after the therapy. This area became infected with hemolytic staphylocci about four weeks after therapy. Meanwhile the residual tumor softened and became smaller, and the patient returned to full consciousness. Continuous improvement of her general and neurological signs was noted until four weeks after the third treatment. However, five weeks after therapy high fever and mental confusion developed.

On May 18, 1959, the patient became cyanotic, and right focal seizures occurred on the right side of her face and right upper extremity. There was no nuchal rigidity. However, suboccipital tap showed a cloudy cerebrospinal fluid. Smear and culture studies of this fluid showed hemolytic staphylococci sensitive to Chloramphenicol (Chloromycetin®). Treatment with Bezanthine penicillin G-streptomycin (Bicillimycin®) and chloramphenicol was started and the patient was placed in an oxygen tent.

On May 19, 1959, on a suboccipital tap approximately 30 cc of pus was aspirated from the right side. After the discovery of this abscess formation, irrigation with 1 to 1000 chloramphenical solution was carried out once or twice

a day for one week. On May 26, 1959 her temperature became normal and the suboccipital fluid was clear. Repeated culture studies of the fluid were negative. The patient was taken out of the oxygen tent and antibiotic treatment was discontinued. With the onset of meningitis she became stuporous and remained in this state after the meningitis subsided, despite the fact that the size of the palpable tumor in the suboccipital area was still progressively decreasing in size. On June 4, 1959 a ventriculogram with dye test revealed complete obstruction of the aqueduct of Sylvius with marked *internal hydrocephalus.* There was no connection between the left lateral ventricle and the suboccipital cyst. Subsequently a daily ventricular tap was required to reduce the increased intracranial pressure.

Around June 23, 1959, ten weeks after the third treatment, it was noted that the patient had peculiar periodic apnea associated with a small amount of gastrointestinal bleeding, progressive mental confusion, and marked spasticity of all extremities. However, by palpation there was only a pear sized resistant nodule in the suboccipital area. This clinical picture suggested some recurrence of the tumor in the deep part of the posterior fossa. It had been established from our previous human and animal experience that treatment of deep-lying tumors requires greater neutron exposure than was obtainable from the Brookhaven Graphite Reactor during the limited interval when the boron-10 is in a critical position.

Meanwhile the Medical Research Reactor was readied for an exploratory therapeutic probe in the late Spring 1959. With this Medical Research Reactor a greater intensity of thermal neutron exposure as well as vastly improved accessibility was available. Preliminary measurements showed a satisfactory thermal neutron flux and did not indicate that a significant gamma exposure would occur in the 3 minutes required to obtain a thermal neutron exposure which was then believed to be a safe maximum. Exploratory therapeutic probes using the Medical Research Reactor on adult patients had previously been carried out uneventfully on May 5, May 25, and June 1, 1959 (8-10).

With the signs suggesting recurrence it was hoped the markedly increased thermal neutron exposures possible with the Medical Research Reactor might permit us to destroy residual tumor close to the center of the cranial vault; therefore the patient received a fourth application of neutron capture therapy, this time in the Medical Research Reactor on June 25, 1959. A dose of 35.1 mg B^{10}/Kg (1,171 mg total boron-10) was given into the antecubital vein over a 5 minute period. Thirty minutes after completing the boron injection, the entire suboccipital area in which the tumor had previously been found was exposed to a heavy thermal neutron cloud for 204 seconds. The Medical Research Reactor was operated at a nominal power of 1 megawatt during this exposure. The thermal neutron flux was 2.36×10^{10} n/cm^2 per second at the skin entrance. The patient received a total of 4.81×10^{12} thermal neutrons per square centimeter at the entrance. The size of the port was the same as before (4 x 5 x 6 inches trapezoidal shape), Table 1.

Following treatment, her general condition was satisfactory but in this particular instance an unusual and unexpected ocular complication developed. Since

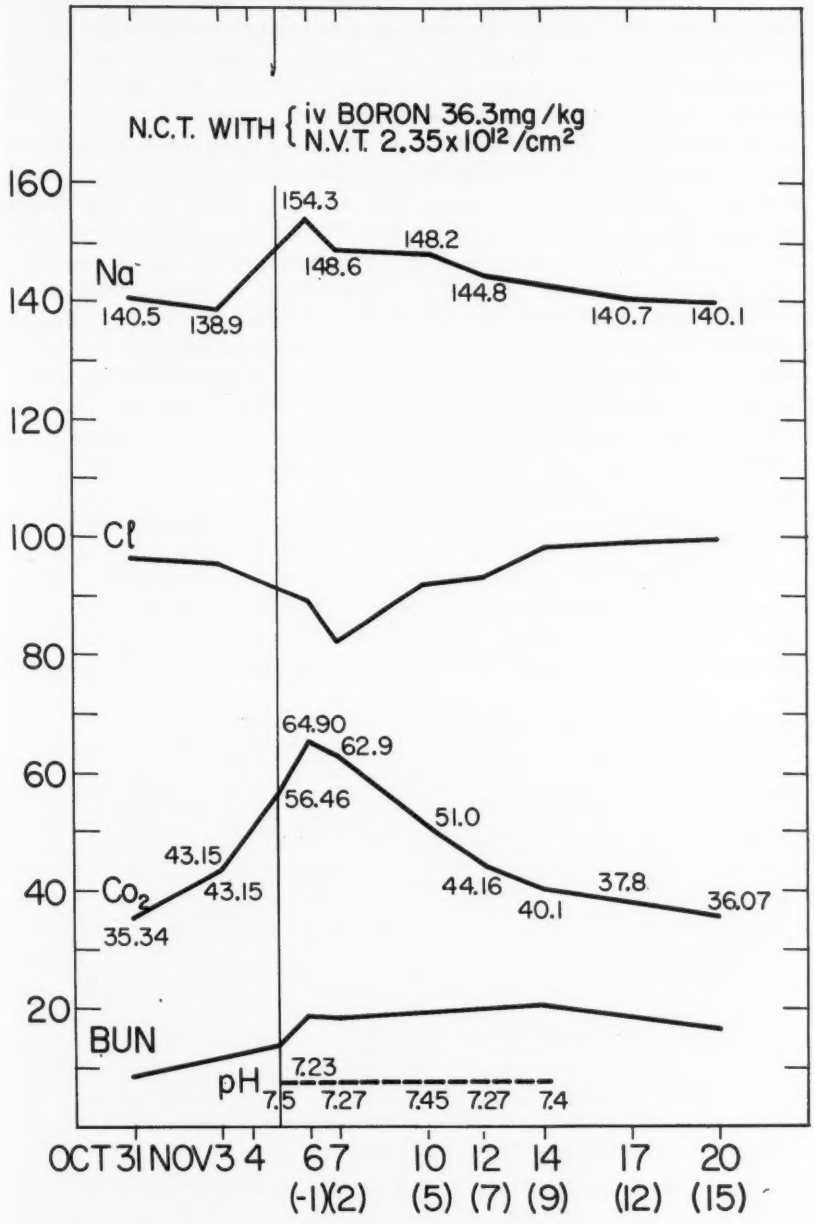

Fig. 4. Graphic demonstration of plasma carbon dioxide content changes in patient following first neutron capture therapy probe.

1952 when local shield of lithium metal and boral were used about the eyes no radiation conjunctivitis had been noted even when temporal to frontal lobes were exposed. It should be noted parenthetically that after boron doses of the amounts used in these treatments conjunctival suffusion is expected. However, in this patient there was a severe conjunctivitis limited to the bulbar conjunctivae which developed within 4-5 hours after therapy. Moderate general facial edema and slight erythema on the upper half of her face were observed shortly after therapy but subsided within the usual five days. The bulbar conjunctivitis, however, became progressively worse for a few days after therapy and marked chemosis with severe vascular injections developed in the bulbar conjunctivae, especially on the nasal side of the left eye, (Fig. 5). A residuum of this bulbar conjunctivitis remained at death one month later. There was no evidence of corneal ulceration or lento-retinal disturbance by ophthalmoscopic examination. The postmortem histological examination showed the superficial layers of conjunctival epithelium to be heavily infiltrated with polymorphonuclear lymphocytes. In some areas these formed micro-abscesses. The subepithelial tissues of the conjunctiva were extremely edematous. They were infiltrated with leukocytes and plasma cells. Small vessels were dilated and congested.

Shortly after treatment a ventricular tap was done and her intracranial pressure was recorded with a pressure transducer intermittently for the next eight days (Fig. 6). For the first 48 hours after the treatment, the ventricular drainage was required almost every 5 to 6 hours, because of rapidly rising intracranial pressure up to 400 - 500 mm water. Approximately 50 to 60 cc of ventricular fluid were removed each time. The frequency of ventricular taps decreased to every

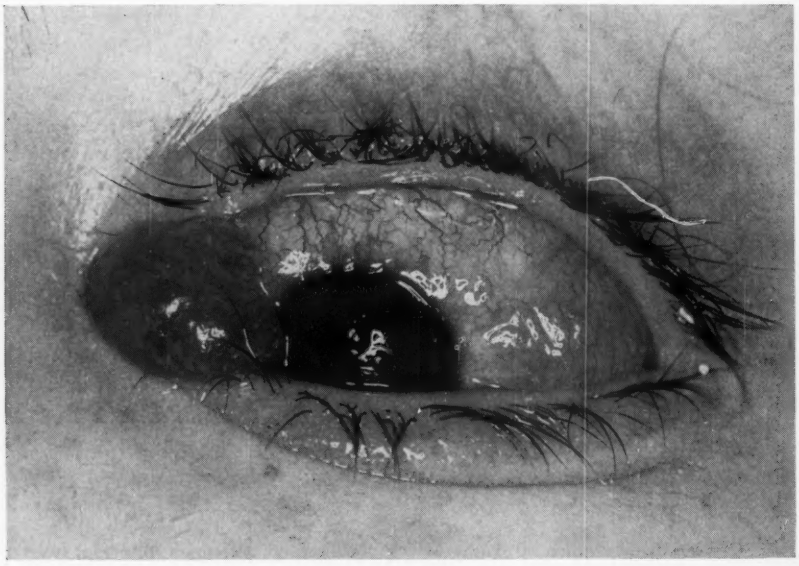

Fig. 5. Post mortem photograph showing persisting conjunctival edema of inner canthus.

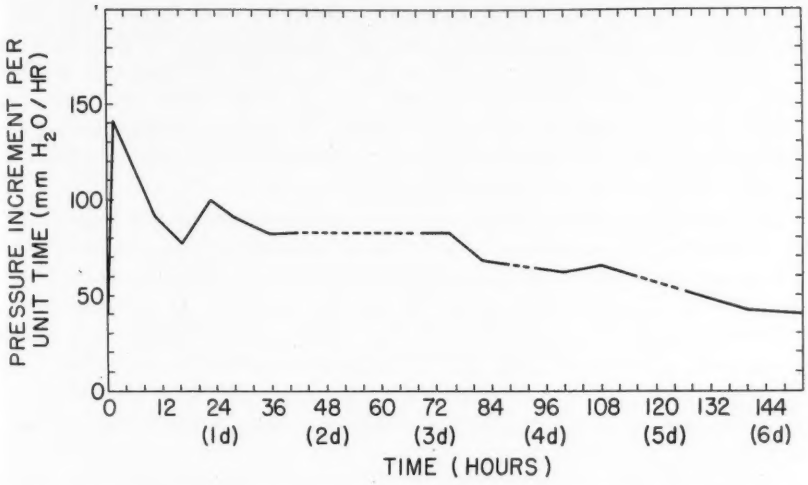

Fig. 6. **Graph showing changes in rate of increase of cerebral spinal fluid pressure for hour after a treatment. Initial and final rates of increase were approximately 40 mm per hour.**

8-12 hours over the next three days. One week after treatment the ventricular dynamic pressure returned to the pretreatment level.

The last remaining superficial palpable tumor on the right side of the suboccipital area became softer and smaller within a week after the fourth treatment, and regressed continuously until death. Approximately two weeks after treatment her mental alertness was somewhat improved for a few days. However, she became stuporous and had severe gastrointestinal track bleeding on July 16, 1959. In spite of repeated blood transfusions her general condition became rapidly worse and she died on July 25, 1959, eight months (262 days) after the first neutron capture treatment. Data of peripheral blood changes following neutron capture therapy are shown in Figure 7. No significant changes were observed in the peripheral blood following neutron capture therapy, but remarkable alteration of peripheral blood changes were observed during periods of hemolytic staphylococcus meningitis, cystitis, and terminal gastrointestinal hemorrhage.

PATHOLOGICAL FINDINGS

A partial autopsy only was permitted in this case. There was a 17 x 15 cm area of atrophic skin in the occiput and posterior neck with complete depilation. A large defect in the occipital bone was the result of the initial operative procedure. No tumor tissue was found grossly or microscopically in the subcutaneous tissue in the occipital and posterior neck areas in which large neoplasms were located prior to neutron capture therapy (Fig. 8). Extensive coagulation necrosis, edematous fibrous tissue with large hyalinized collagen fibers and foreign body giant cells were found in the dermis and subcutaneous tissue

in this area (Fig. 9). The meninges of the area of the bone defect were thick and fibrotic. The basal meninges were slightly thickened. Gyri of the cerebrum were flattened and bilateral uncus herniation was present. There was marked hydrocephalus with dilatation of lateral ventricles and third ventricle. The posterior inferior one fifth of the right cerebellar hemisphere contained extensive liquified necrotic tissue which dropped off from the brain at the autopsy. No neoplastic tissue was found in this mass.

The sagittal sections of brain stem and cerebellum showed a large friable well demarcated tumor mass, 2.5 x 4 cm in diameter, located in the fourth ventricle and extending deeply into the dorsal half of the pons and caudal midbrain (Fig. 10). In this area (A in Fig. 10) the neoplastic tissue was densely cellular and similar in appearance to that of the initial biopsy, but a few necrotic areas were present (Fig. 11). In the ventral part of the cerebellum there was an encapsulated and hyalinized mass measuring 1.3 cm in diameter, and closely adjacent to it, a similarly appearing mass, 0.5 cm in diameter. These

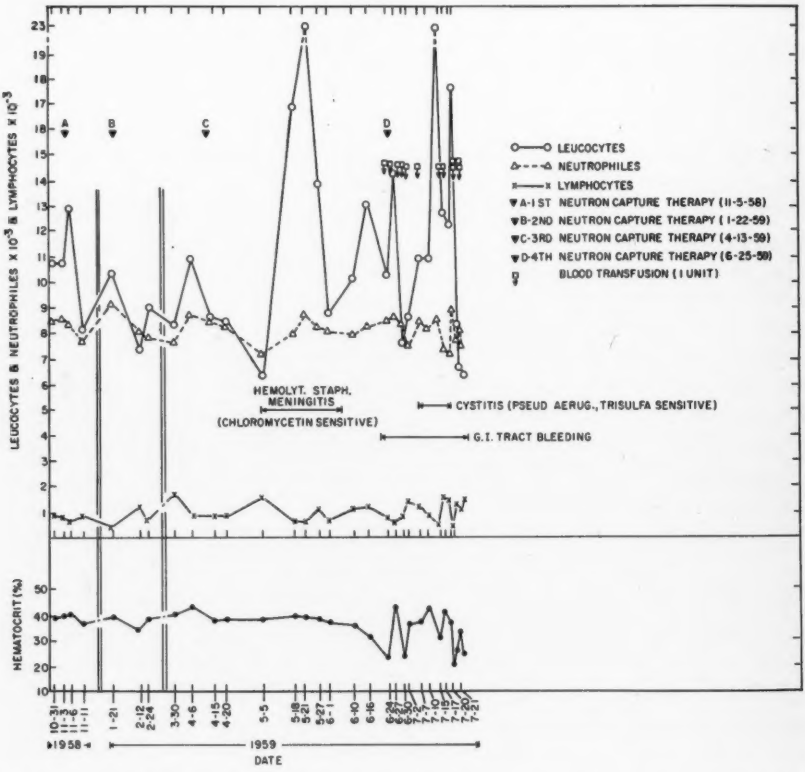

Fig. 7. Peripheral blood changes following neutron capture treatments. Remarkable alteration of peripheral blood changes were only observed periods of meningitis, cystitis and G.I. tract bleeding.

nodules (B in Fig. 10) were composed of necrotic tissue consisting of numerous leucocytes, erythrocytes, phagocytes and fragments of nuclei, and were surrounded by thick friable tissue containing numerous plasma cells (Fig. 12). Between these two areas there were multinucleated giant tumor cells with bizarre appearance scattered among the small neoplastic cells. Posterior to the nodules (B in Fig. 10) there was extensive gliosis and disappearance of numerous Purkinje cells. No neoplastic tissue was present in this area.

Another significant finding in the limited autopsy materials was atrophy with striking infiltration of plasma cells in the cervical and mesenteric lymph nodules and spleen. The pituitary gland, both adenohypophsis and neurohypophysis, appeared normal.

DISCUSSION

Treatment in this instance with neutron capture therapy was gratiyfingly effective in eliminating nearly all of the presenting tumor mass. Furthermore, this destruction of malignant tissue was accomplished without disturbance of function of adjacent and intervening normal structures of the central nervous system. The fact that a much lesser degree of control was established by previous conventional radiologic therapy is of interest. It suggests that neutron capture therapy may under appropriate circumstances, be highly efficient and that previous failure to control a neoplasm by maximum x-ray therapy does not

Fig. 8. Photograph of the occiput and posterior neck at autopsy. The operative bone defect is shown. Note the absence of neoplasm in the cervical region where initially it was most marked.

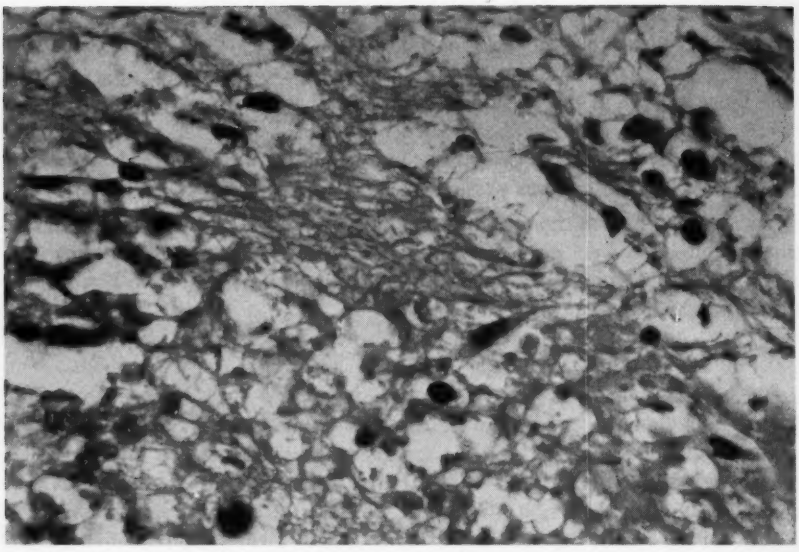

Fig. 9. Histology of neoplasm in the subcutaneus tissue on the posterior neck at time of autopsy. Compare with Figure 1. X 400.

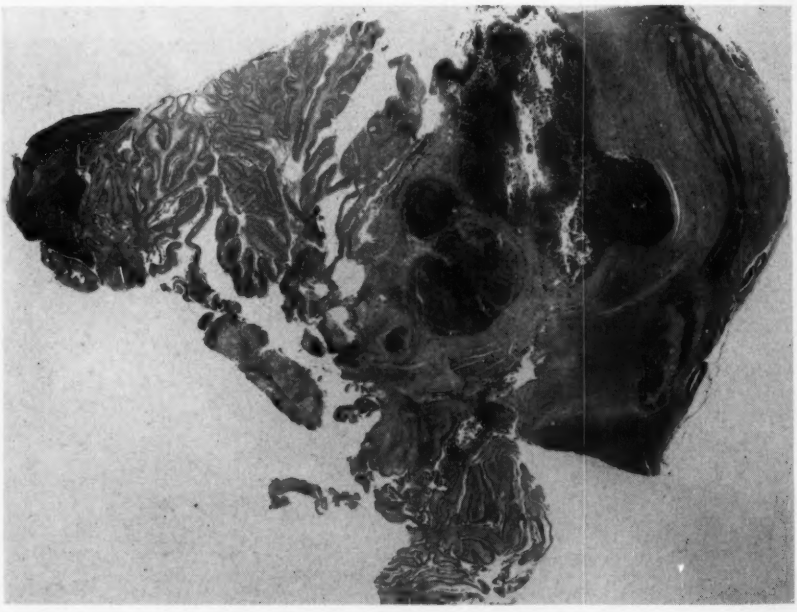

Fig. 10. From sagittal sections of the cerebellum and brain stem. A well demarcated neoplastic mass (A) occupied the entire fourth ventricle, extending to the dorsal part of the pons and the caudal midbrain. Two small necrotic masses (B), surrounded by fibrotic and hyalinized tissue were located in the ventral part of the cerebellum.

necessarily indicate that the tumor will fail to respond in the same way to neutron capture therapy.

Several points should be clarified. The necrotizing dermatitis that was noted over the central port area after the first treatment was a calculated risk. The difficulties of turning back a satisfactory and viable skin flap in a patient in such precarious condition warranted postponement of skin preservation to a later date when grafts could be resorted to if indicated. Patients subsequently treated with skin flaps turned back have had most satisfactory healing of the flap and no evidence of injury to the presenting surfaces of the cerebral cortex. The extremely sharp boundaries of necrotizing neoplasm at the edges of the neutron exposure area have been seen in all patients and animals treated by this technique. This apparent all or none response would not be expected on the basis of neutron attentuation or boron distribution. This complex problem is mentioned here only to state that in a subsequent communication considerable evidence on this point will be adduced. The failure to eliminate the deepest seated remnant of the neoplasm would appear to be an attentuation effect on the thermal neutron cloud as it penetrates tissue. This is consistent with the noted increasing effectiveness at depth only when the neutron flux is increased. Because of the type of response which has been consistently noted, multiple treatments have been no more effective than single exposures. In this instance while four exposures were given, the direction of maximum penetration differed in each, as did the exposure field. Thus significant neoplastic masses received only a single exposure even though four treatments were given.

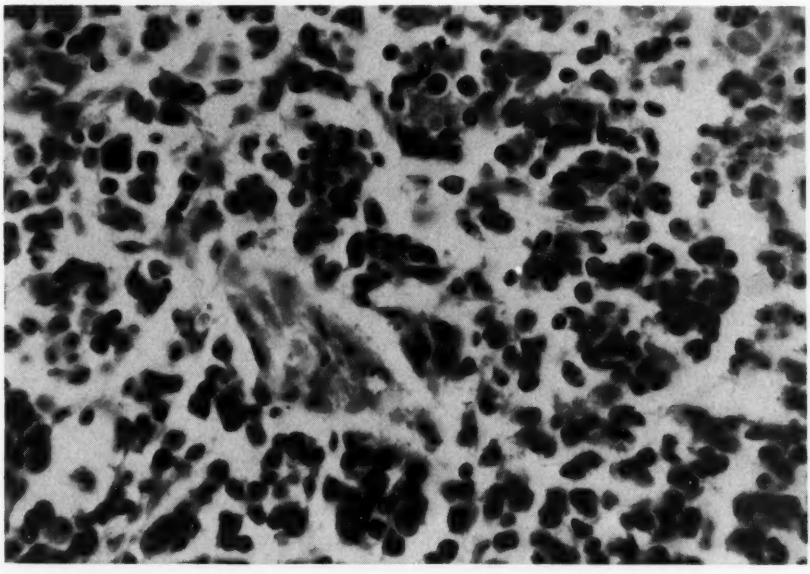

Fig. 11. Histology of neoplastic mass (A) in pons similar appearance as the initial biopsy. X 300.

The development of bulbar conjunctivitis, apparently as a result of the capture reaction being provoked by *emergent* neutrons, was a totally new and unexpected phenomenon. It suggested to us that the entering neutron cloud contained significant numbers of neutrons of intermediate energies which need to be reduced to prevent recurrence of this complication. Steps have been taken to alter the moderator system to accomplish this. The extremely high discrimination between the various structures of the eye and between the different conjunctival membranes is noteworthy. This selectivity, as inferred earlier, we found to be quite characteristic of this therapeutic approach.

Finally, while complete control was not established, the degree of palliation effected is highly encouraging to us. Serial sections of the brain remain to be studied further to establish the innocuousness of the procedure, when it is properly carried out.

SUMMARY

A patient with a highly malignant vascular sarcoma of the cerebellum was treated by neutron capture therapy. Almost complete elimination of the neoplasm was attained. Other than the skin, normal tissues about and within the neoplastic mass did not appear to be adversely affected. An unusual and unexpected bulbar conjunctivitis was observed as a complication. The degree of control attained by this experimental procedure was more positive than that previously attained by surgery or conventional x-ray therapy. This is the first attempt

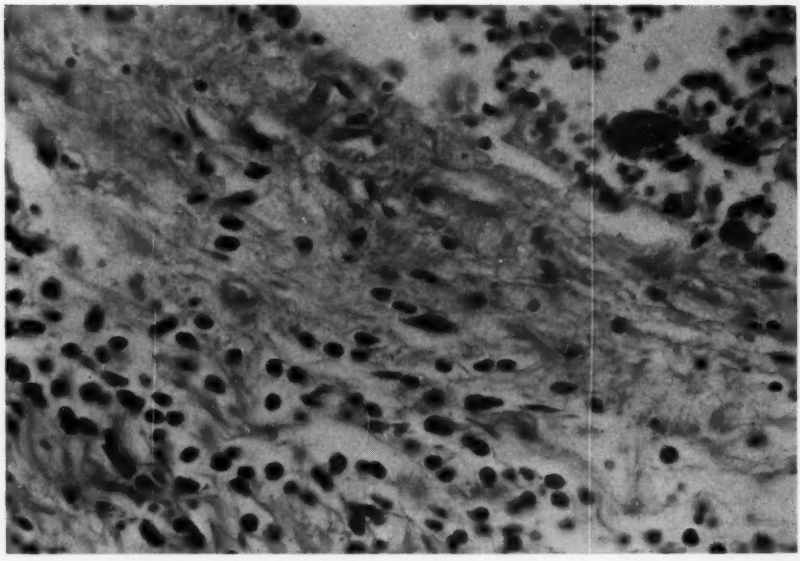

Fig. 12. Histology of necrotic nodules (B) in the ventral part of the cerebellum. The necrotic tissue consisted of numerous leucocytes, erythrocytes, phagocytes and fragments of nuclei. These necrotic masses were walled off by connective tissue containing numerous plasma cells.

to control an intracranial tumor other than glioblastoma multiforme by this procedure.

The patient is noteworthy for the extreme retention of carbon dioxide, 60 milli-equivalents per liter in the blood, apparently resulting from functional disturbances of the respiratory center.

ACKNOWLEDGEMENTS

The authors wish to express their gratitude to Doctors Robertson, Stickley, Fine, Lippincott and Easterday; to Mr. Konikowski, Miss Ripperger, Miss Driscoll, Miss Straub and other members of the technical staffs for their assistance in various studies of significant facets relating to the neutron capture therapy of this patient.

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JOURNAL OF NUCLEAR MEDICINE 2:272-281, 1961

Renal Scintiscans in the Diagnosis of Renal Vascular Disease[1]

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Along with recent interest in renal hypertension, there has been a search for better diagnostic tests for renal vascular disease. The radioisotope renogram has been of use but one of its main deficiencies is a lack of anatomic information. The development of photoscanning techniques and new radioactive labeled compounds has made it possible to scintiscan the kidney. Both I^{131}-Hippuran (1) and Hg^{203}-Neohydrin (2) have been successfully employed for renal scanning. We wish to report the application of scintillation scanning to the problem of renal vascular disease.

TECHNIQUES

I^{131}-Hippuran: The technique described previously was employed for performing I^{131}-Hippuran scintiscans (1). Two hundred μc of I^{131}-Hippuran was infused at 2-4μc per minute, and 20 minutes after starting the infusion, scanning was begun and continued for 30-40 minutes.

Hg^{203}-Neohydrin: An intravenous dose of 100 μc Hg^{203}-Neohydrin was employed and scanning was begun 40 minutes after injection.

Scanning Equipment: A photoscanning device (3) with a 19-hole collimator and a 3″ × 2″ sodium iodide crystal has been employed.[2]

RENAL INFARCTION IN DOGS

Scintiscans were made of dog kidneys in vivo before and after surgical segmental renal vascular occlusion as described previously (4). The results in only one dog will be presented here.

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Supported by a grant from the Phoenix Memorial Project of the University of Michigan #200 and the Atomic Energy Commission Project #15.

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[2]Picker Magnascanner, Picker X-Ray Corp., White Plains, New York.

Figure 1 compares a scan obtained employing I^{131}-Hippuran (Fig. 1A) to a scan after Hg^{203}-Neohydrin (Fig. 1B), 30 days after right lower segmental renal artery occlusion. A subsequent necropsy demonstrated a 2 × 3 cm infarction of the right lower pole. Both I^{131}-Hippuran and Hg^{203}-Neohydrin demonstrated decreased uptake in the lower pole of the right kidney. The larger renal outline with Hg^{203} is due to better cortical delineation.

APPLICATION IN HUMANS

Renal scintiscans have been performed on 40 patients suspected of having renal hypertension. We wish to detail our findings in 14 of the 40 patients who were subsequently demonstrated at surgery to have renal vascular lesions. Five patients had unilateral and five had bilateral renal artery stenosis. Eight patients had atherosclerotic occlusions of the renal arteries. One patient had unilateral intimal fibrosis and one had an aneurysm of a segmental artery. One patient had bilateral renal cysts and possibly had renal ischemia due to pressure on contiguous vessels. Four patients had segmental lesions. For the most part no long term conclusions can be drawn regarding the response to renal vascular surgery in these patients as all patients have been operated upon during the past 10 months.

The accuracy of each preoperative diagnostic procedure has been evaluated in regard to ability to detect significant ischemia or infarction and to distinguish unilateral from bilateral disease. If the operative or pathologic findings fitted with the results of the diagnostic test, the test result was said to be "correct". If the test did not do what might be expected of it in predicting the true nature of the lesions, then the test was said to be "incorrect".

Renal scintiscan results are compared with other diagnostic procedures in Table 1.

The Hg^{203}-Neohydrin scintiscans were correct in 8 out of 10 instances, or 80 per cent. The procedures ranked in order of decreasing accuracy are aortograms, Hg^{203}-Neohydrin scintiscans, I^{131}-Hippuran renograms, pyelograms, the Howard test and finally I^{131}-Hippuran scintiscans.

From the analysis of these cases it would appear that no procedure is infallible in the diagnosis of renal hypertension, and that each test has its own contribution to make. The case summaries of four patients, presented below, illustrate some of the interesting problems encountered in the detection of renal vascular disease.

CASE REPORTS

Case #1

Comparison of I^{131}-Hippuran and Hg^{203}-Neohydrin Scintiscans in the Same Patient.

Patient S. E., was a 50 year old white male with hypertension of 8 years duration, not improved by splanchnicectomy in 1954. His blood pressure was 260/140 mm Hg. The usual renal function tests were normal. An I^{131}-Hippuran renogram revealed bilateral abnormality most marked on the left and split func-

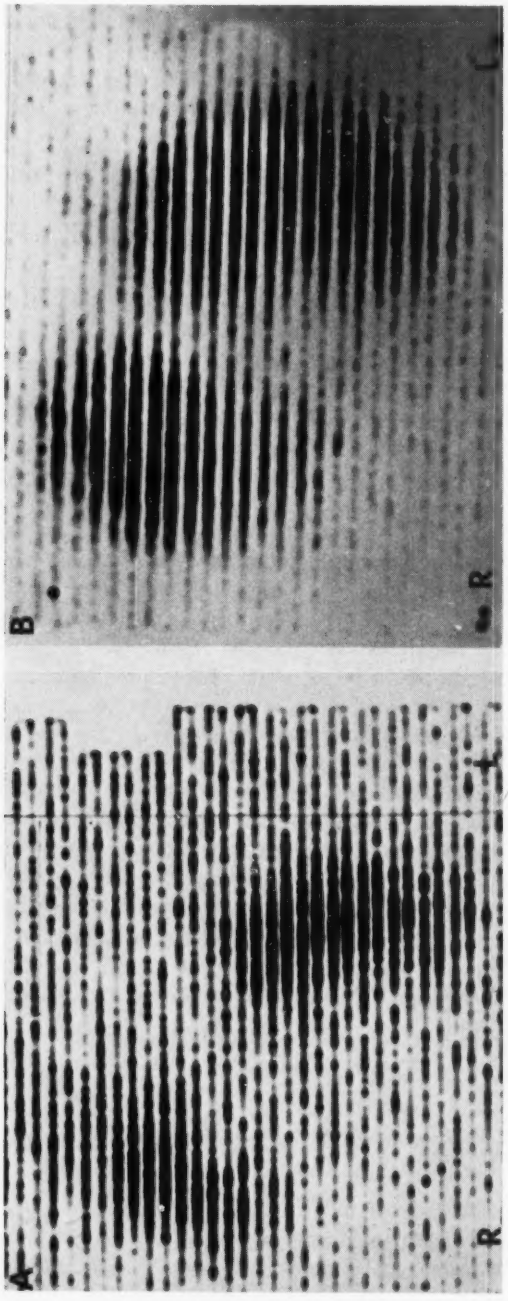


Figure 1A and 1B: Photoscans performed with I^{131}-Hippuran (A) and Hg^{203}-Neohydrin (B) in a dog 30 days following experimental production of a 2 x 3 cm segmental infarction in the lower pole of the right kidney. Note the decreased concentration of radiosotope in the lower pole of the right kidney with both techniques.

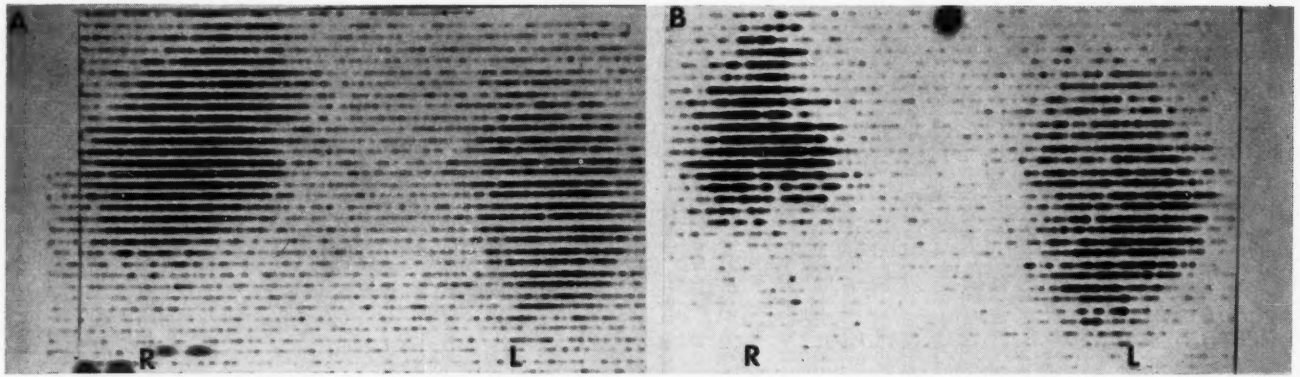


Figure 2A and 2B: Photoscans in a patient with bilateral atherosclerotic stenosis of the main renal arteries, most marked on the left. Hg^{203}-Neohydrin (A) demonstrated decreased concentration on the left while the right kidney is relatively normal. I^{131}-Hippuran scan (B) demonstrated a "radiopyelogram" on the right and a full renal outline in the more ischemic left kidney.

tion studies (Howard test) revealed an 80 per cent decrease in urine volume and a 30 per cent decrease in sodium excretion from the left kidney. A transfemoral aortogram was unsuccessful and a trans-lumbar aortogram revealed a stenosis of the left main renal artery and no filling of the right main renal artery. An intravenous aortogram revealed bilateral renal artery stenosis most marked on the left. The renal scintiscan performed with Hg^{203}-Neohydrin (Fig. 2A) revealed general reduction in radioactivity in the left kidney while the right appeared normal.

On the other hand, I^{131}-Hippuran (Fig. 2B) revealed a full renal shadow on the left and a small dense "radiopyelogram" on the right. Partial atherosclerotic occlusion of both renal arteries was found at operation. This patient had a left aorto-renal bypass with transient drop in blood pressure, but six months after operation the blood pressure was 210/110, probably related to disease on the contralateral side. Neither scintiscan was called "correct" in this case because neither suggested bilateral disease.

Summary: The usefulness of I^{131}-Hippuran scans has been sharply curtailed by the conflicting findings in ischemia and infarction. As illustrated by this case, casual review of the I^{131}-Hippuran scan suggests segmental vascular infarction of the right kidney. Actually the contrast media is all in the pelvis at the time of the scan, while the ischemic left kidney is well outlined by the slower passage of I^{131}-Hippuran. The mercury scan more clearly suggested left renal vascular disease. This case also illustrates how difficult it is to demonstrate impaired renal function in the "good" kidney in the presence of predominantly unilateral renal vascular disease.

Case #2

Functional Change Distal to Renal Arterial Stenosis.

B. C. was a 45 year old white male with hypertension of 15 years duration and a recent malignant course (blood pressure 220/150 and papilledema). Renal function tests revealed one plus albuminuria, 15 minute PSP excretion of 15 per cent and creatinine clearance of 67 liters per 24 hours. The I^{131}-Hippuran renogram and Howard tests did not suggest unilateral abnormality. Intravenous pyelograms were normal. However, a transfemoral aortogram suggested a stenosis at the origin of a segmental artery from the aorta to the lower pole of the left kidney (Fig. 3A).

The Hg^{203}-Neohydrin renal scintiscan did not suggest any segmental abnormality in the left kidney and indeed was not particularly abnormal (Fig. 3B). At operation there was an aberrant artery and an atherosclerotic plaque at the origin of the lower segmental artery to the left kidney. Direct pressure readings did not reveal any fall in pressure distal to the plaque, however, and therefore a bilateral splanchnicectomy was performed and no renal surgery was carried out.

Summary: In this case an aortographic finding suggesting possible segmental ischemia was not supported by scintiscanning and proved to be insignificant.

Case #3

Detection of Residual Viable Tissue.

L.H. was a 37 year old white female who had known hypertension of two years duration. In March of 1959 an aortogram had revealed a stenosis of the right renal artery. Following the resection of the narrowed portion and the substitution of a Teflon graft, the blood pressure was normal until September 1960 when an attack of right flank pain was followed by recurrence of hypertension. The renal function tests were normal. Intravenous pyelograms revealed non-visualization of the right kidney and the I^{131}-Hippuran renogram (Fig. 4A) revealed no uptake of radioactivity over the right kidney.

On split function study (Howard test) no urine was obtained from the right side. An I^{131}-Hippuran renoscan (Fig. 4B), however, revealed a faint but definite area of uptake in the lower pole of the right kidney. A right nephrectomy was performed and indeed the kidney was totally infarcted except for a small area of viable tissue measuring 3 × 4 cm at the lower pole of the right kidney. The patient has been normotensive for 8 months following this operation.

Summary: The renal scintiscan has been the most sensitive test for the detection of small areas of viable tissue in our experience.

Case #4

Detection of Space Occupying Lesions.

R.G. was a 45 year old white male with hypertension of 6 years duration, a history of left renal calculus in 1950, and a blood pressure of 210/160. Renal function studies were normal. A Howard test did not suggest unilateral renal disease, and an intravenous pyelogram was read as normal (Fig. 5A).

A transfemoral aortogram was interpreted as showing decreased vascularity in the upper pole of the left kidney. The renoscan (Fig. 5B) only suggested an abnormality of the upper pole of the left kidney, but there was a definite filling defect of the lateral border of the right kidney. An intravenous aortogram then revealed a large cyst of the right kidney and a smaller cyst in the upper pole of the left kidney. At operation a right renal cyst measuring 5 cm and a left renal

TABLE 1.

RENAL VASCULAR DISEASE
COMPARATIVE ACCURACY OF DIAGNOSTIC PROCEDURES

	Number of Cases	*Number of Correct Diagnoses*	*Percent Correct*
Aortograms	13	11	85
Hg^{203}-Neohydrin Renal Scintiscans	10	8	80
Renograms	13	9	69
Pyelograms	14	8	57
Howard Test	11	6	56
I^{131}-Hippuran Renal Scintiscans	6	1	17

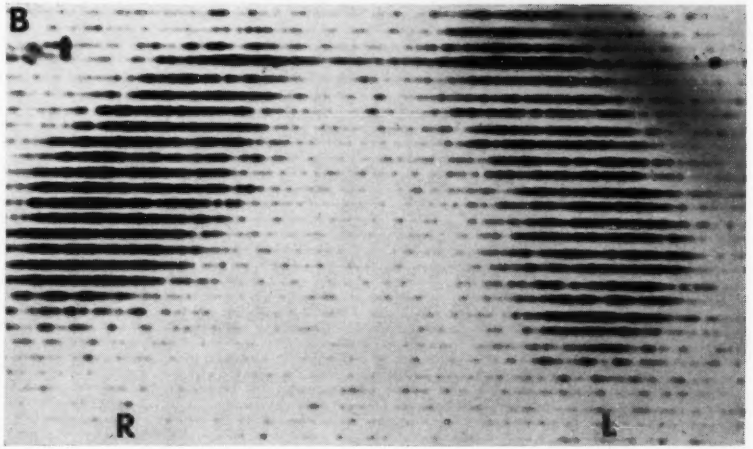
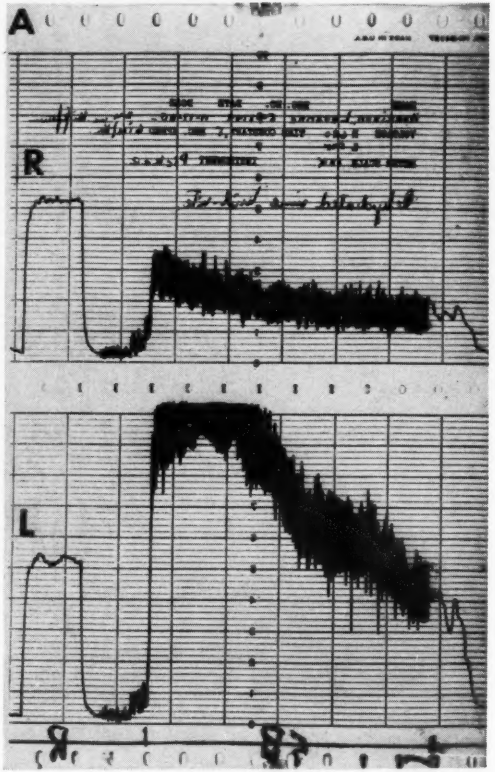


Figure 3A and 3B: The transfemoral aortogram (A) in this hypertensive patient showed an aberrant artery to the lower pole of the left kidney with a stenosis at its origin. The Hg^{203}-Neohydrin renal scintiscan (B) did not suggest segmental ischemia in this area of the left kidney and this was proved correct at operation.



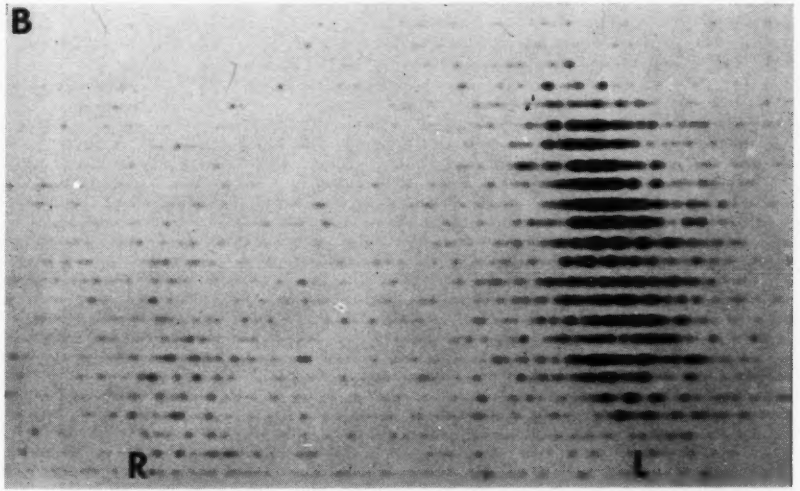


Figure 4A and 4B: Patient with an infarction of the right kidney where the renogram (A) suggested a non-functioning right kidney and split function studies produced no urine from the right side. I^{131}-Hippuran renal scintiscan (B) indicated a small area of viable tissue in the right lower pole and this was confirmed at operation.

cyst measuring 3 cm were unroofed and post-operatively the blood pressure fell to normal. On a return visit 3 months later the pressure was 150/105 mm Hg.

Summary: This case illustrates the versatility of the renal scintiscan in that a patient referred for possible vascular abnormality was found to have a space-occupying lesion. Routine radiographs including a transfemoral aortogram were not interpreted as showing the large cyst on the right.

DISCUSSION

From the experience reported here we feel that the diagnostic accuracy of Hg^{203}-Neohydrin renal scintiscans compares favorably with the other procedures

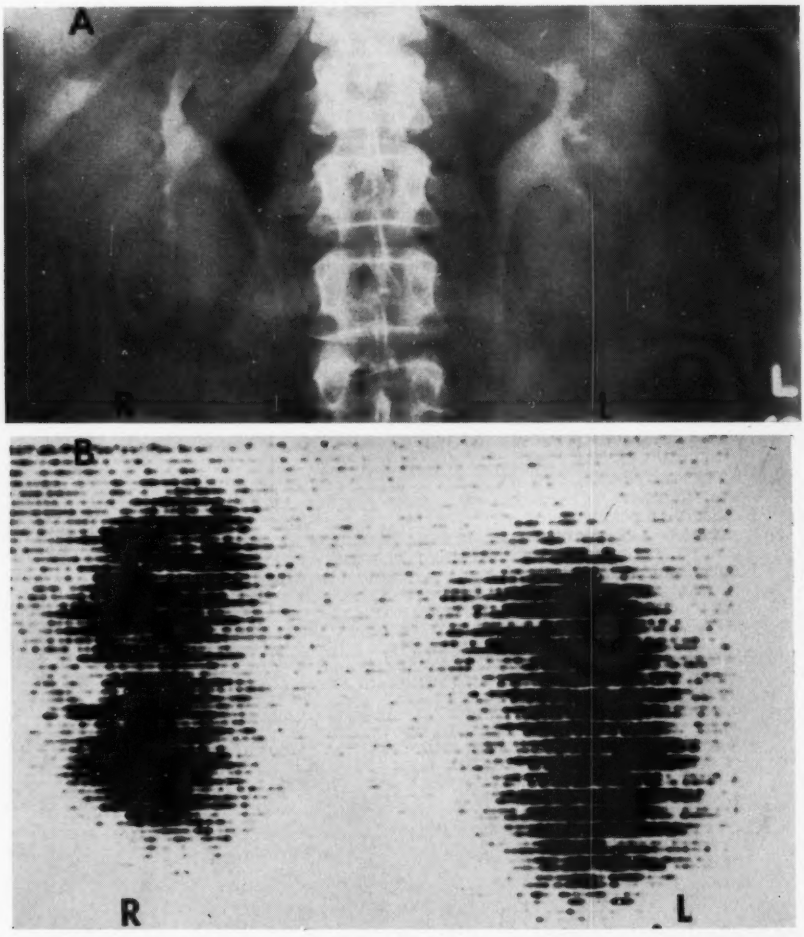


Figure 5A and 5B: Intravenous pyelogram (A) in this hypertensive patient and transfemoral aortogram were not interpreted as showing a large 5 cm renal cyst in the right kidney (laterally) which was revealed by renal scintiscans (B) and confirmed at operation.

currently used in the diagnosis of renal hypertension. Although the series is small, reference is made only to surgically proven cases.

In these cases, I^{131}-Hippuran renal scintiscans have been evaluated and found wanting. Even if technical improvements could be made in performing the scans, it is questionable whether this technique would be superior to routine roentgenographic techniques, as I^{131}-Hippuran is a contrast media.

Hg^{203}-Neohydrin scintiscans have been quite promising. They have correctly predicted the operative findings in a high percentage of cases (80%). Since one does not see the renal vessels with renal scintiscans, this technique cannot replace aortography in determining the location and type of arterial lesions. On the other hand, renal scintiscans seem very effective in evaluating the functional significance of arterial lesions, in detecting small areas of viable tissue (where it appears to be the most sensitive technique available), and disclosing space-occupying lesions.

SUMMARY AND CONCLUSIONS

Renal scintiscans using Hg^{203}-labeled Neohydrin and photoscanning have been demonstrated to show segmental infarction in the dog kidney in vivo. Renoscans performed with Hg^{203}-Neohydrin have correctly predicted the operative findings in a high percentage (80%) of 14 surgically documented cases of renal vascular disease in hypertensive patients. The ranking of renal scintiscans with other procedures in order of decreasing accuracy in detecting renal vascular disease was 1) aortograms, 2) Hg^{203}-Neohydrin renoscans, 3) renograms, 4) pyelograms, 5) Howard test, and 6) I^{131}-Hippuran renoscans. Renoscans have proven particularly useful in evaluating the functional state of renal tissue distal to arterial lesions, detecting small areas of viable tissue, and in revealing space-occupying lesions. I^{131}-Hippuran renal scintiscans have been disappointing. The addition of anatomic information to the radioisotope procedure in the evaluation of renal vascular disease patients has proven fruitful in a small series of cases and deserves further application.

ADDENDUM: Since submitting this paper for publication, we have examined two patients with renal scintiscans having stenosis of a main renal artery, and the scintiscans showed a small kidney but no fall in the concentration of Mercury^{203}-Neohydrin, when compared to the unaffected side. Both of these patients were operated upon, and a fall in blood pressure was found distal to the area of stenosis. Corrective surgery was performed with restoration of blood pressure to normal. It appears, therefore, that significant ischemia of a kidney can exist without reduction in the concentration of Hg^{203}-Neohydrin.

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JOURNAL OF NUCLEAR MEDICINE 2:282-288, 1961

The Preparation and Use of I^{131} Labeled Sulfobromophthalein in Liver Function Testing[1]

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INTRODUCTION

Certain tests of hepatic function are based on the ability of the polygonal cells to remove specific types of dyes from the blood and to excrete these via the biliary tract. By labeling the dyes with I^{131} and using appropriate instrumentation, the rates of organ uptake, blood disappearance and excretion can be measured externally. The radioactivity of these dyes permits the use of very small quantities, thereby avoiding occasional toxicity. It also obviates the difficulties of colorimetric measurement regardless of the level of jaundice, even in severe liver damage. The data obtainable permit evaluation of liver function and aid in the diagnosis of disorders of that organ and its excretory systems.

Sulfobromophthalein (BSP) has been used in colorimetric clinical procedures, with modifications, since 1925 (1) to test liver function. Since that time much knowledge has been accumulated concerning the clinical use, excretion and metabolism of the dye.

Rose Bengal, a somewhat similar dye labeled with I^{131} was introduced by Taplin et al. in 1955 (2). The radioactivity permitted the measurement of the excretion of the dye by the liver by counting over that organ to produce curves of the dynamics of liver uptake and excretion versus time. Later this technique of external counting was modified by Blahd and Nordyke (3), who measured the blood disappearance by monitoring a large stable vascular bed, namely the lateral aspect of the head at contact.

These radioisotopic methods eliminate the technical difficulties associated with the colorimetric procedures and are able to detect changes in subacute and chronic liver disease.

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It was felt that the ideal substance would be one that has a rapid blood clearance, is capable of external measurement and shows a distinct increase in biliary excretion into the intestine after milk or cholecystokinin. Sulfobromophthalein labeled with I^{131} seemed to meet these criteria, especially since much information was already available concerning the excretion and metabolism of unlabeled BSP and its use in the assessment of liver function.

It is presumed, as described below, that the I^{131} is attached to either of the two types moieties in the sulfobromophthalein molecule, depending upon the treatment. It is thus not truly a labeled BSP, although the iodine is stably bound.

Since BSP is somewhat similarly constituted, it might be a comparative material for the study of Rose Bengal I^{131}. Brauer et al. (4) prepared BSP labeled with S^{35} for studies of its distribution and excretion but this isotope does not permit external measurement.

METHODS

BSP was labeled with I^{131} in this laboratory by two methods producing two dyes differing in their iodine content and physico-chemical properties but with similar biological behavior.

In Method 1, an adaptation of that of Myers (5), 1 ml of 1:9 HCl:H_2O in a 15 ml centrifuge tube was heated in a water bath to 80°. To this, 0.025 ml (81 mg.) (0.5mM) Iodine Monochloride was added and thoroughly mixed. To this tube, then placed in a hood with adequate ventilation and shielding, was added 20 mc NaI^{131} in a small volume and all were mixed by bubbling with a Pasteur pipette. The temperature of the bath was lowered to 65° and to this solution was added 210 mg (0.25mM) Sulfobromophthalein Sodium in 1 ml H_2O and 0.6 ml 0.1N NaOH, mixed by bubbling and maintained at ca. 65° for 2 hours. After this period, the mixture was evaporated to dryness in a small porcelain dish on a water bath. The residue was then dissolved in 1 ml H_2O plus 1 ml N NaOH and added dropwise to 60 ml ice-cold acetone contained in a 125 ml Erlenmyer flask equipped with a 1.5 inch magnetic stirring-bar, in an ice bath. At first the magnet was not operated, permitting large aggregates to form, then was operated slowly until all the BSP solution had been added. The flask was stirred slowly for 30 minutes in the ice bath. The contents of the flask were then equally divided in 2 heavy wall centrifuge tubes and centrifuged at 2500 rpm for 15 min. to pack the precipitated dye. The supernate was carefully removed and set aside for decay and disposal. The precipitates were washed by resuspension in 10 ml ice cold acetone and recentrifuged, the acetone removed as above. The tubes were now placed in a vacuum desiccator and dried for 2 hours or more to constant weight.

In Method 2, the I^{131} was introduced by "exchange" for some of the bromine in the BSP. This was analogous to method used for exchanging I^{131} for I^{127} in sodium iodohippurate. (6). In this method ca. 20 mc I^{131} was released from NaI^{131} solution by 0.33 ml 0.01M KI, 0.1 ml M $NaNO_2$ and 0.2 ml 2.5 M HCl and the iodine shaken out with 2 ml CCl_4. The shakeout was repeated with the same quantities of reagents but no I^{131}. The combined CCl_4 solutions were washed by shaking with 2 ml H_2O, then extracted with 0.5 ml H_2O plus 0.6 ml 0.1 M NaOH followed by 0.5 ml H_2O plus 0.5 ml 0.02M NaOH. The extracted NaI^{131} was added to 210 mg BSP dissolved in 1 ml H_2O plus 0.6 ml 0.1 M NaOH in a 10 ml serum vial. The vial was closed with a rubber stopper covered on its underside with a Saran film, sealed with an aluminum seal and heated to 70-75° for 1 hour. The contents of the vial were evaporated to dryness, redissolved in 1.5 ml H_2O and added drop-wise to 50 ml ice-cold acetone, centrifuged, washed and dried as under Method 1.

RESULTS

The properties of the two $BSPI^{131}$ compounds are summarized in Table 1.

TABLE 1. COMPARISON OF PROPERTIES OF BSPI^{131} MADE BY 2 METHODS

Preparation	*Method 1*	*Method 2*	*BSP HWD*	*NaI^{131}*
Color	Blue	bluish-purple	bluish-purple	
Maximum absorption in 0.1 N NaoH, mμ	575	595	595	
Maximum Specific Activity in μc/mg	137.8	85.5		
% Iodine[7]	7.9	5.3		
Probable no. atoms I/molecule dye	0.81	0.37		
R_f, ascending, in n-butanol:H_2O:acetic ac. 1.48:1:0.37 by volume, on Whatman 3MM paper[a]	0.69	0.62	0.58	0.97[b]
R_f, ascending, in tert-butanol:H_2O 1.73:1 v/v, on Whatman 3 MM paper[a]	0.95	0.91	0.91	0.75[b]
R_f, descending, in "0.5M Phosphate buffer"[9] on Whatman No. 1 paper[c]	0.79	0.87	0.89	0.77[b]

a. Modified from Grodsky et al. (8)
b. By radioautography
c. McMillion & Brown Dunning (9)

The BSPI^{131} made by Method 1 contained a slight amount of NaCl and was standardized against a sample of the pure dye, precipitated from a dilute solution so as to minimize salt precipitation, by constructing a concentration versus transmittance curve at 575 mμ using the Coleman Universal Spectrophotometer Model 14. The BSPI^{131} prepared by Method 2 was similarly standardized against commercial BSP at 595 mμ. Subtle chemical and biological differences of the two dyes are being investigated. It is presumed that in BSPI^{131} of Method 1, the iodine is in the phenolic rings ortho to the hydroxyl groups and in BSPI^{131} of Method 2, that an exchange reaction has taken place between (I^{127} plus I^{131}) and some of the bromine atoms in the tetrabromophthalic moiety.

Solutions for parenteral use were made to contain approximately 50 μc/ml by dissolving the requisite amount of dye, after standardization for dye content and activity. The dye was dissolved in sterile pyrogen-free distilled water, the pH of the solution adjusted to 7, filtered through a fritted filter, bottled in sterile,

pyrogen-free bottles, sealed with aluminum seals and sterilized in boiling water for 30 minutes.

Chromatographic analysis and radioautography before and after sterilization and storage showed only a trace or no unbound I^{131}.

ANIMAL STUDY

A tracer dose injected into a normal rabbit gave a blood disappearance $T_{½}$ of 5.5 minutes based on blood radioactivity, as compared to 2.5 minutes for Rose Bengal reported by Taplin et al. (10). The blood radioactivity as measured over the lateral aspect of the head on contact and the liver uptake curves are shown in Fig. 1.

In B., the curves have been displaced to start at a common point of origin (100 c/s) to permit a direct comparison of the rates of change of dye radioactivity in the liver and head. The counting rate over the thyroid was very low, indicating little free iodine present or formed by metabolism in about 1 hour.

HUMAN STUDIES

Normal subjects and patients were injected with approximately 30 μc of $BSPI^{131}$ prepared by either method since it had been shown that the biological behavior of the dyes was similar. Separated by at least 1 day, just prior or

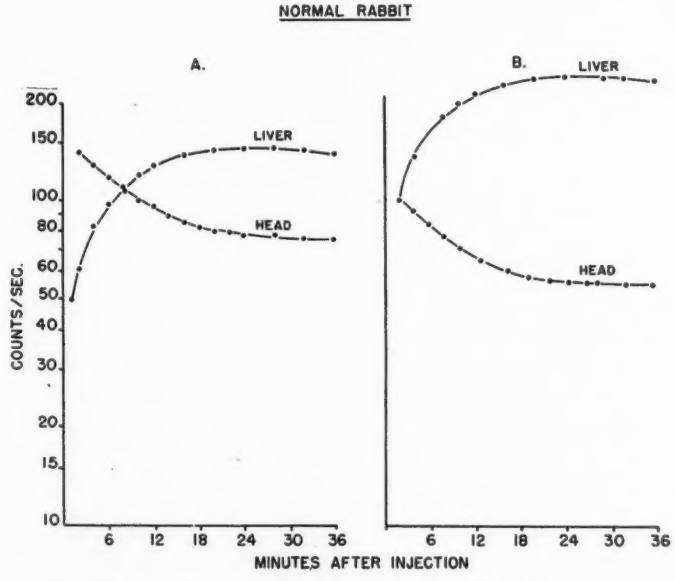

Fig. 1. A. Curves obtained by plotting counting rates obtained at the head and over the liver following injection of tracer dose of $BSPI^{131}$.

B. The curves have been displaced so both have a common point of origin. (See Text.)

subsequently, the normals and patients were injected with tracer doses of Rose Bengal I^{131} (RBI^{131}) following a 6 to 16 hour fast.

After injection of either $BSPI^{131}$ or RBI^{131}, serial counting rates over the head and abdomen were determined simultaneously. The probe placed over the lower left quadrant of the abdomen consisted of a 1½ × ¾ inch NaI (T1) crystal with a 4 × 7 inch shield and 3⅜ inch port. The head probe was a 1 × ¾ inch crystal with a 1 inch shield and a 2½ inch port. Counts were read from a standard scaler every 2 to 5 minutes alternately from each probe, for periods up to 60 minutes. In some patients, blood samples were taken every 3 minutes for periods up to 60 minutes.

Milk given by mouth, at about 30 minutes after the injection of the $BSPI^{131}$, or cholecystokinin by injection, induced gall bladder emptying indicated by a rise in the radioactivity in the lower left quadrant of the abdomen.

It was found that the blood and head count disappearance rates parallel each other at the early times but in the normals, the curves diverge at about 16 minutes. In several studies 1, 6 and 24 hour urines were collected and 24-hour thyroid radioiodine uptake tests were made, to study the excretion and metabolism of the dye.

Quantitation of the rate of disappearance of the $BSPI^{131}$ from the blood was made by comparing the head (blood) count at 5 minutes and at 20 minutes and calculating the 20 minute retention as a percentage of the 5 minute retention. This had been found to be 40 to 50 per cent for Rose Bengal I^{131} and was adopted as the arbitrary standard (11). Five normal subjects had ratios of 40 to 51 per cent and these agreed with their RBI^{131} ratios within a few per cent. Three other normals showed a wider variation in the ratios using $BSPI^{131}$ and RBI^{131}. Two cirrhotics showed good agreement, the ratios being 59 and 89 per cent for RBI^{131} and the corresponding $BSPI^{131}$ ratios being 69 and 90 per cent. Two jaundiced patients had very similar RBI^{131} and $BSPI^{131}$ ratios. In a single case of cancer of the pancreas the RBI^{131} ratio was 75 per cent and the $BSPI^{131}$ ratio was 95 per cent.

TABLE 2. EFFECT OF LOADING WITH UNLABELED BSP ON THE DYE RETENTION OF A NORMAL SUBJECT.

Dye Used	*Date*	*Mg Dye in Dose*[a]	*Mg Dye as Loading*	*% Dye Retention*[b]
Rose Bengal I^{131}	6–24–59	1.0	0	56
$BSPI^{131}$	6–17–59	1.5	0	45
$BSPI^{131}$ + BSP	7–1 –59	4.5	200	47
$BSPI^{131}$ + BSP	7–8 –59	9.9	400	47
$BSPI^{131}$ + BSP	7–14–59	15.0	600	53

a. Dose = 30 μc

b. $\%\ \text{Dye Retention} = \dfrac{\text{20 min. count}}{\text{5 min. count}} \times 100\%$

EFFECT OF STRESSING WITH UNLABELED BSP

It was felt by Taplin et al. (10) and Carbone et al. (12) that placing the liver under stress by the simultaneous administration of large doses of BSP to "load" the polygonal cells, would increase the sensitivity of the test. To test the effect of loading, two normal subjects were simultaneously injected with doses of unlabeled BSP ranging from 100 to 600 mg and with $BSPI^{131}$ in doses from 1 to 15 mg, equivalent to 30 μc. Loading resulted in delayed excretion, and the 20 to 5 minute ratio increased from 45 to 53 per cent in one normal, at the 600 mg level of BSP and from 38 to 55 per cent in another at the 500 mg level. This is shown in Table 2 for a normal subject M., J., with the per cent dye retention using RBI^{131} for comparison.

These results are qualitatively similar to studies reported by Taplin and co-workers (10) on normal and CCl_4–poisoned rabbits and normal human subjects, using tracer doses of RBI^{131} and unlabeled BSP.

In our studies, the thyroid count and the 24 hour-urinary excretion of I^{131} was low for normals and much higher for cirrhotic and jaundice patients, using $BSPI^{131}$ and RBI^{131}. Treatment with Lugol's solution and propylthiouracil made little difference in the retention ratios.

THE USE OF $BSPI^{131}$ FOR THE STUDY OF BSP METABOLISM

Another important use for a labeled agent is in the study of the metabolic and excretory channels and processes of the liver. Present information indicates that BSP is detoxicated and conjugated with cysteine and glutathione in the liver (8), (13).

The metabolism of $BSPI^{131}$ was studied in a jaundiced patient who was undergoing biliary drainage. A tracer dose of 50μc (1.27 mg) $BSPI^{131}$ was administered and simultaneous blood (head) counts were made and 3 minute bile samples were taken for 1 hour. His retention ratio was 77 per cent. The bile obtained during the 21 to 61 minute period was combined and analyzed for $BSPI^{131}$ and its conjugates by paper and alumina column chromatography according to the methods of Grodsky et al. (8) The radioactivity of the bile rose sharply for the first 38 minutes and then remained at a high level for the next 22 minutes. The radioactivity of the bile seemed to be due mostly to unmetabolized $BSPI^{131}$ but it contained also small amounts of two separate and distinct radioactive metabolites. Their R_f values of 0.48 and 0.23 on Whatman 3 MM paper using the n-butanol etc. solvent in Table 1, ascending, were determined from their radioautographs. It is planned to investigate and characterize these compounds further.

DISCUSSION

In the preparation of the $BSPI^{131}$ by Method 2, "exchange" with NaI^{131} at pH 6.5, lower specific activity dyes were obtained indicating that an alkaline pH seems to favor the exchange.

The results of this preliminary study indicate that the biological behavior of the two $BSPI^{131}$ dyes is similar to that of unlabeled BSP and they are removed

from the blood in a similar manner to RBI^{131}. BSPI^{131} may be of value in elucidating the pathways of liver uptake, metabolism and excretion and thus enhance the accumulated body of knowledge now available concerning BSP. Further studies will be undertaken to isolate and characterize the radioactive metabolites of BSPI^{131}.

SUMMARY

Radioiodinated BSP has been prepared by two methods to yield two dyes of sufficiently high specific activities to permit external measurement of their disappearance from the blood. These dyes have distinctly different physico-chemical properties but similar biological behavior. Preliminary data indicate that the dyes are removed rapidly from the blood and excreted via the liver and biliary tract. Very little of the injected activity appears in the urine of non-jaundiced patients and about 1.5 per cent of the radioactivity of the injected dose is found in the thyroid after 24 hours. The advantages of the use of these dyes are that only tracer quantities are required, obviating occasional toxicity, and that the I^{131} label may be of great value in the study of the metabolism of the dye.

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JOURNAL OF NUCLEAR MEDICINE 2:289-296, 1961

Practical Application of Neutron Activation Analysis for the Determination of Protein Bound Metals in Blood Serum[1]

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The necessity for determining the presence of low levels of copper and manganese in blood serum for the solution of certain clinical diagnostic problems is well documented in the literature. The detection of these minute quantities by neutron activation analysis offers a sensitive method and, until now, a rather complicated one (1-6).

In neutron activation analysis, a small quantity of a material is exposed to the neutron flux of a nuclear reactor. Many of the stable isotopes present in the material are activated, or made radioactive, and may be identified in a scintillation spectrometer by virture of their characteristic gamma radiation and half lives. Using a comparison sample of known amount of the investigated element and treating it in a manner similar to the unknown sample, it is possible to make a quantitative and qualitative analysis. The sensitivity of the technique is determined, among other things, by the neutron flux, neutron cross section, half-life, and efficiency of the counting system. Since the primary purposes in this project were to achieve accuracy, simplicity and practicality, no special effort was made to obtain maximum sensitivity although values of 10^{-8} to 10^{-9} grams of copper and manganese in blood serum samples were measured.

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[1]Work performed by the Radioisotope Service, Veterans Administration Hospital, Hines, Illinois in cooperation with the Argonne National Laboratory, Argonne, Illinois. Work performed, in part, under the auspices of the U.S. Atomic Energy Commission.

[2]Radioisotope Service, Veterans Administration Hospital, Hines, Illinois.

[3]Argonne National Laboratory, Argonne, Illinois.

PROCEDURE

1. Container preparation.

The containers used in the reactors must be non-metallic, must not leach appreciable contaminants from the walls to the blood serum during the test, and must be easily and thoroughly sealed. Polyethylene[a] tubing for such containers was prepared by cleaning successively with xylene, ethyl alcohol, distilled water, dilute HNO_3, distilled water, and dried immediately prior to loading with serum. Evidence of leaching existed as ascertained by the presence of small amounts of activated contaminants measured in water left standing in these tubes for 30 minutes. These amounts were less than 1% of the counts measured from the blood serum and were considered negligible for this analysis.

2. Standard preparation.

Electrolytically pure metallic copper was dissolved in a small volume of concentrated HNO_3 and diluted to one liter with water of the type used for intravenous injection.[b] The latter was found to be practically free of all objectionable elemental contaminants (much better than triple-distilled H_2O). The concentration of copper/ml. in the standard was adjusted to be similar to that measured in blood serum.

The manganese standard was prepared by dissolving 0.0510 gm. $MnSO_4 \cdot H_2O$ into one liter I. V. water.

3. Serum preparation.

The presence of activated sodium and other inorganic ions complicates the spectral analysis. These ions were removed by dialyzing the blood serum against 0.04m ammonium barbital buffer for a minimum of 24 hours. Blood serum samples of 2 ml. volumes were placed in a tied visking bag in this buffer at pH of 8.6. The buffer was changed three times while in a refrigerator for this period and agitated with a teflon-covered magnetic stirrer.

AVERAGE OF FOUR DETERMINATIONS

	Albumin	α_1	α_2	β	γ
Control	51.9	3.6	9.9	15.3	20.2
Dialyzed	50.3	3.6	10.9	15.6	19.5

Values are percent of total.

Figure 1: Electrophoresis results of dialyzed serum.

[a] "Polyflo", Imperial Brass Co., Chicago, Illinois.
[b] Baxter Laboratories, Morton Grove, Illinois.

The contents of the visking bag, which increased during dialysis, were transferred to a clean volumetric flask and brought up to 10 ml. with the I. V. water. Samples were removed with volumetric pipettes and transferred to the cleaned polyethylene tubes, one end of which had been heat-sealed. After filling, the open end was heat-sealed and samples numbered by etching the tube wall.

4. Reactor tube loading and activation.

The "rabbit" tube at the Argonne CP-5 reactor was utilized for this study. The samples were subjected to a flux of about $7x10^{12}$ n/cm^2-sec. for periods of 15 minutes to 1 hour depending upon the conditions of the experiment. Each rabbit tube, a lusteroid capsule, was loaded with 3 standards of Cu and Mn each and 2 samples of blood serum.

The samples were removed from the reactor and the lusteroid "rabbit" container discarded. The activity level of the polyethylene containers and samples was in the mrem/hour range and presented no special handling problem.

5. Counting procedure.

1 ml. aliquots were removed from each tube and placed into plastic test tubes for counting. The polyethylene material showed irregular, but small, amounts of Na^{24}, which prevented counting of serum directly in the original container.

Counting was done by two different methods:

a. On a single channel, continuously recording anlyzer utilizing a 2x2 NaI (Tl) crystal. Resolution of 16% (Cs^{137}) was achieved and counting rates of 5,000 to 20,000 cpm were commonly encountered over the Cu and Mn peaks with a window of about 1 volt.

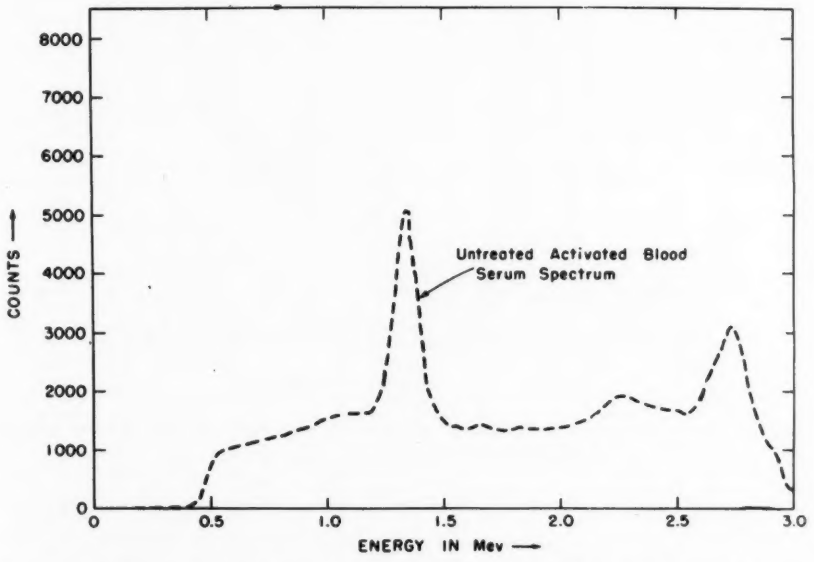

Figure 2: Spectrum of activated undialyzed blood serum obtained with 256 channel analyzer.

b. On a 256 multichannel analyzer utilizing a 5x4 crystal in an iron-shielded room. Better resolution and efficiencies were available here permitting identification of more elements and more accurate quantitation.

Quantitation was achieved by planimeter measurements of areas under the peaks after visually subtracting the Compton background. These areas were compared to the standards and reproducible readings obtained.

Another procedure for quantitating the final number was employed in which the spectra of unknown and standards were obtained separately on the ANL 256 channel analyzer. The results were analyzed by dividing the unknown spectra into convenient regions of interest. Corresponding fractional contributions of the various standards were determined for these regions and algebraic linear simultaneous equations were set-up and solved to quantitate the unknowns. Presence of additional elements was ascertained by use of the multichannel analyzer where a sensitivity gain of about 1000 was available. With this sensitivity, decay studies were feasible 4 to 5 days after activation.

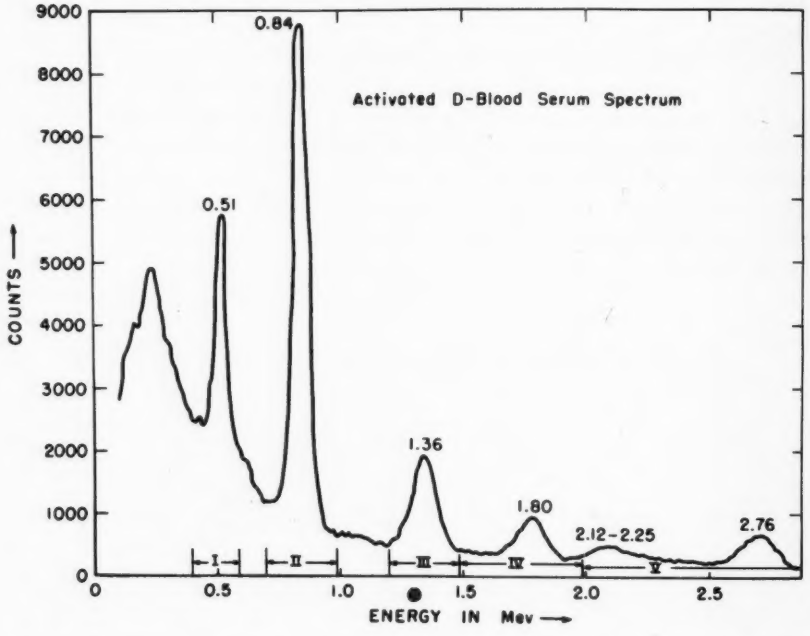

Figure 3: Spectrum of activated dialyzed blood serum obtained with 256 channel analyzer.

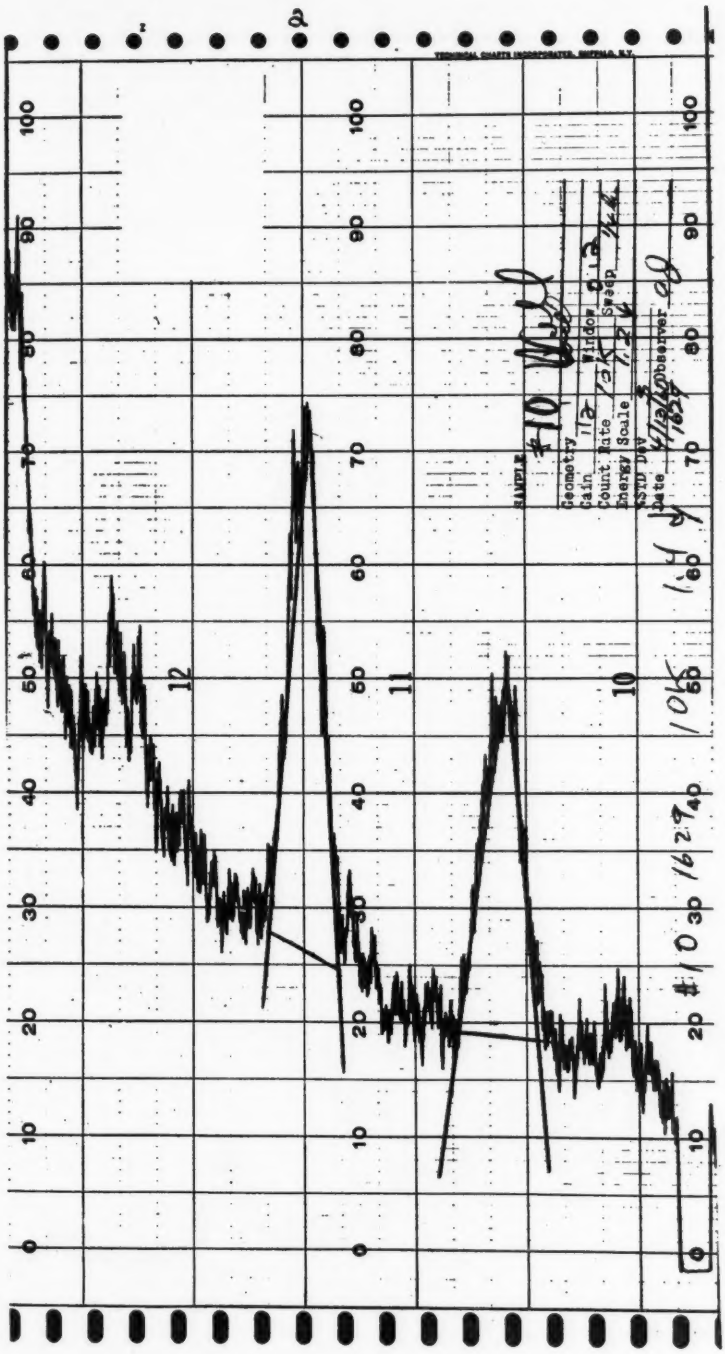

Figure 4: Spectrum of activated dialyzed blood serum obtained with single channel recording spectrometer.

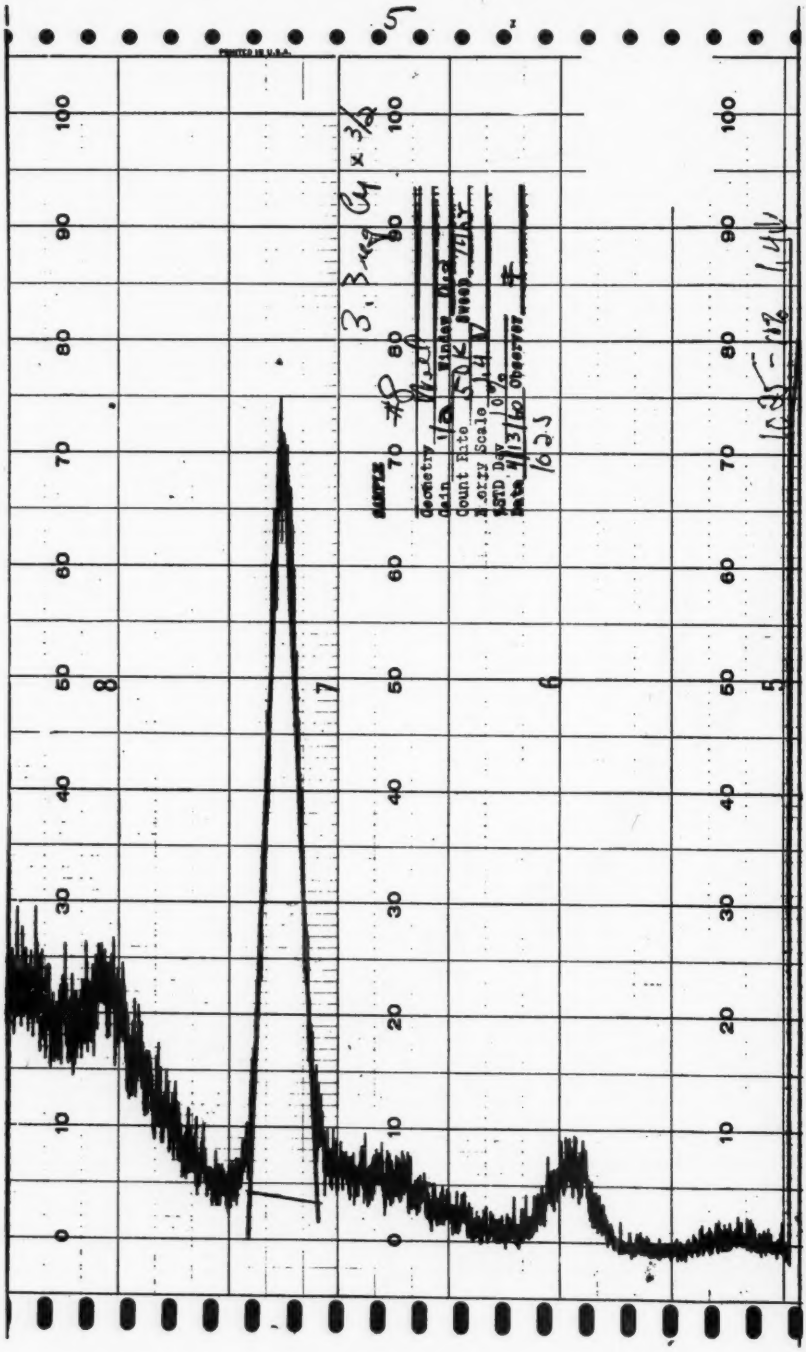

Figure 5: Spectrum of Cu^{64} standard obtained with single channel analyzer.

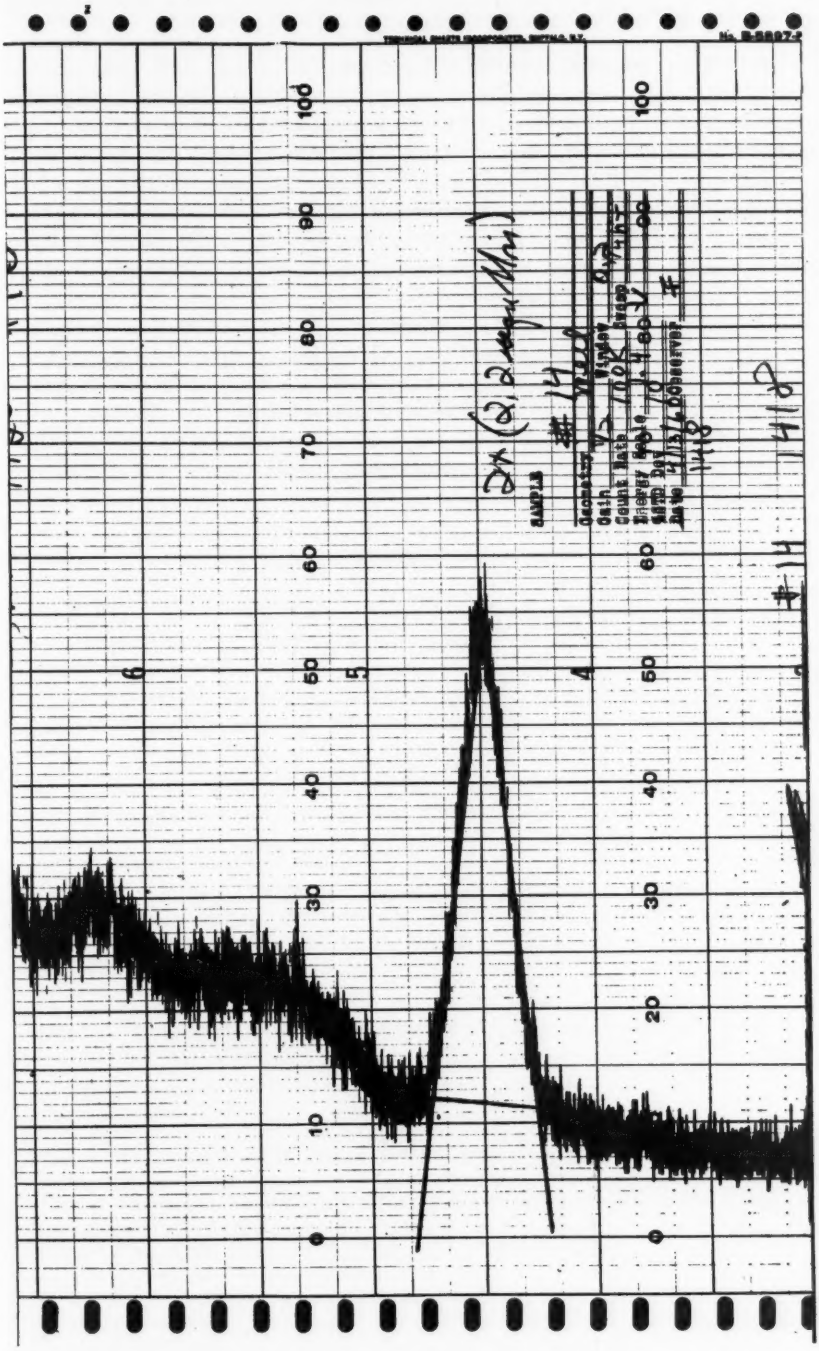

Figure 6: Spectrum of Mn^{56} standard obtained with single channel analyzer.

RESULTS

Essentially complete removal of sodium, potassium and chlorine was achieved. Complete retention of protein was maintained as shown in Figure 1. Ion exchange separation techniques which were tried were notably poor in this instance because of loss of protein on the ion-exchange column.

Untreated, undialyzed, blood serum spectrum was observed to have a high Na^{24} background (Figure 2) as contrasted to the treated (dialyzed) blood serum spectrum (Figure 3). Figures 2 and 3 were obtained with a 256 channel analyzer while a spectrum obtained from a treated blood serum sample on a single channel analyzer is seen in Figure 4.

Counts from Cu^{64} and Mn^{56} standards were in the 5-20,000 cpm range and accuracies of $\pm$ 10% were estimated for each individual sample (Figures 5, 6). Mn^{56} samples were counted shortly after irradiation because of the relatively high activity as compared to Cu^{64} which could be counted the following day.

Results of tests performed on the serum of normal patients by this procedure yielded the expected values of approximately 2μg/ml serum for copper and 0.1μg/ml serum for manganese.

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Anemia of Nontropical Sprue Studied with Radioiron and Radiochromium[1,2]

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Despite the fact that anemia complicating sprue has been recognized for decades, relatively little is known about its development. However, with the introduction of radioactive isotopes in clinical and experimental medicine, some progress has been made in elucidating a few of the important factors that are involved. With the exception of the report of Badenoch and Callender (1), most work reported to date has been concerned with the role of malabsorption of vitamin B_{12}.

The exact incidence of anemia associated with sprue is unknown. In the recent study of Green and Wollaeger (2) on 124 cases encountered at the Mayo Clinic, the incidence of anemia was 60 per cent. These authors accepted less than 12 gm. of hemoglobin per 100 ml. of blood to represent anemia, a figure which we used in our study. The frequency varies depending on the severity of the disease, but it is probable that anemia occurs in all untreated patients at some time during the course of the disease.

Read at the meeting of the Society of Nuclear Medicine, Estes Park, Colorado, June 23 to 25, 1960.

1. From the Sections of Medicine and Biochemistry, Mayo Clinic and Mayo Foundation.
2. Abridgment of portion of thesis submitted by Dr. Giuliani to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Medicine.
3. The Mayo Foundation, Rochester, Minnesota, is a part of the Graduate School of the University of Minnesota.

It is our purpose to report on the pathogenesis of anemia of sprue studied with isotopes of iron (Fe^{59}), chromium (Cr^{51}) and cobalt (Co^{58}) in vitamin B_{12}, with special emphasis placed on the role of metabolism of iron.

In the present investigation, 65 studies were carried out on 40 persons. The patients with sprue represent an unselected group in whom the clinical diagnosis was confirmed by laboratory studies. All patients showed evidence of a "deficiency pattern" of the small bowel on x-ray examination and evidence of malabsorption of fat and other nutrients.

METHODS AND MATERIALS

Absorption of Iron. A standard test dose, 50 micrograms of iron labeled with one microcurie of radioiron plus ascorbic acid (3), was given to each person 2 or more hours after the morning meal. Each person drank the solution as well as the rinsings from a plastic cup and was asked to fast for 2 hours. Less than 0.1 per cent of the radioiron adhered to the cup.

Specimens of stool were collected in a standard waxed carton and the radioiron content was measured directly (3). Stools were collected until a 24-hour collection contained less than 1 per cent of the administered dose.

In order to check on the accuracy of the fecal recovery method, blood was drawn on the fourteenth day after oral administration of the radioiron in 12 normal persons and the radioactivity in the circulating erythrocytes was determined. The total radioiron in the erythrocytes in this group was calculated on the basis of a whole blood volume of 70 ml per kilogram of body weight. The sum of the radioiron in the circulating erythrocytes and in the feces ranged from 87 to 108 per cent of the oral dose, with a mean rate of 96 per cent.

Radioiron and Radiochromium Administered Intravenously. Twenty milliliters of blood was obtained from each patient; 10 ml was heparinized and up to 14 microcuries of radioiron as ferrous citrate with a specific activity ranging from 3.6 to 7.68 microcuries per milligram of iron was added. To the other 10 ml of blood, 2 ml of Strumia ACD (citric acid, sodium citrate, and dextrose) solution was added along with not more than 400 microcuries of radiochromium as sodium chromate. The specific activity of the radiochromium ranged from 27.1 to 46.2 millicuries per milligram of radiochromium.

The blood containing the radioiron was well mixed and allowed to stand for 30 minutes. Five milliliters of the blood mixture was returned to the patient intravenously. An aliquot of the remaining portion was used in preparation of a standard.

Samples of blood were obtained from the patient at 10-to-15 minute intervals over the next hour and the amount of radioactivity in the plasma of each sample was determined. The data obtained were plotted semilogarithmically and the time for disappearance of half of the injected radioiron ($T\frac{1}{2}$) was calculated.

During this procedure the mixture of radiochromium and blood was gently agitated periodically. At the end of 1 hour, 35 mg of ascorbic acid was added to reduce the residual chromate ion and thus block further labelling with radiochromium (4). Five milliliters of this radiochromium-labeled blood was injected

intravenously. A standard was made from an aliquot of the remaining portion. After a 15-to-20 minute interval, to allow uniform mixing of the radiochromium, a sample of blood was withdrawn and used to determine the blood volume by means of the following equation:*

$$\text{Whole blood volume} = \frac{A - (B \times C)}{D - (E \times F)}$$

In this equation A equals the counts per second (c/s) in total milliliters of whole blood; B, counts per second in milliliters of plasma; C, 1 — 0.96 x hematocrit of blood (plasmacrit) x milliliters of whole blood; D, counts per second in patient's whole blood sample; E, counts per second per milliliter of plasma; and F, 1 — 0.96 x hematocrit of blood (plasmacrit) x the milliliters of patient's blood counted.

Blood samples were drawn every 2 or 3 days by means of a heparinized syringe. The hematocrit was determined for each sample and corrected for trapped plasma (5). After thorough mixing, 4 ml of the sample was pipetted into an appropriate tube for scintillation-well counting. The cells were lysed with powdered saponin and each tube was covered with a rubber cap to prevent evaporation and was set aside for counting. All samples were compared with the standard prepared at the beginning of each study.

The greater energy of the gamma rays of radioiron was discriminated from the weaker energy of gamma rays of radiochromium in order to distinguish the radioactivity of the two substances as described by Weinstein and Beutler (6).

Although total iron binding capacity was not measured in all cases, it was felt on the basis of two studies that the amount of iron added probably did not exceed the total iron binding capacity. These two patients had a total iron binding capacity of 360 and 372 micrograms per 100 ml of serum and a serum iron level of 84 and 93 mg per 100 ml, respectively; since less than 1 microgram of iron was added per milliliter of plasma, a wide range of tolerance was present.

Subjects.—Absorption of iron was quantitated in 17 patients (seven women and 10 men) with nontropical sprue, and in 19 normal persons (four women and 15 men). Six patients with nontropical sprue received test doses combined radioiron and radiochromium by intravenous injection.

RESULTS

The absorption of 50 micrograms of iron by 19 normal persons (Table 1) agrees well with that reported by Bonnet and co-workers (3); slightly less than half the dose was absorbed by men and slightly more than half by women.

The absorption of iron by patients with nontropical sprue (Table 2) averaged 18 per cent, with a range of 1 to 35 per cent of the oral dose. The distribution of these values, as well as those of the controls, is shown in Figure 1.

*This indirect method was compared with the direct method (washing of erythrocytes) in one patient with a difference in the results of less than 2 per cent.

The difference between the mean values of the two groups was greater than two standard deviations. The difference becomes more pronounced when the normal persons and the patients with nontropical sprue are divided according to sex (Table 3).

The reduced ability of patients with sprue to absorb iron is even more striking when their tendency toward anemia and their low concentrations of iron in the serum are considered. Seven of the eight patients with sprue who absorbed as much as 21 per cent of the oral dose of iron had hypochromic anemia. Although this degree of absorption of iron is at the lower limit of the normal range, it is much lower than would be expected in a normal person with a similar degree of anemia.

TABLE 1.

ABSORPTION OF RADIOIRON (PER CENT OF 50-MICROGRAM DOSE) IN NORMAL SUBJECTS*

Age, years	*Hemoglobin, grams/100 ml of whole blood*	*Erythrocytes, million/1 cu mm*	*Iron, micrograms/100 ml of serum*	*Hours after eating*	*Per cent of oral dose of iron absorbed*
Women:					
22	12.1	—	109	2½	39
54	13.4	—	130	2½	49
26	13.2	—	52	3	60
22	11.9	—	96	3	68
Men:					
26	14.3	—	120	2½	20
28	14.8	5.2	218	2–3	24
27	14.6	4.8	130	14	25
27	14.8	—	92	2½	27
25	13.5	—	110	2½	31
29	13.2	4.3	168	2½	33
34	14.3	4.5	95	1½	33
30	14.1	5.0	90	2½	35
27	14.2	4.5	90	2–3	35
28	13.9	5.5	170	2½	39
29	13.9	4.5	99	2½	40
26	13.4	4.0	142	2–3	48
31	13.5	4.5	189	2–3	61
28	14.6	5.2	79	14	69
30	13.7	4.8	57	2–3	72

*Absorption was calculated by subtracting the amount of radioiron excreted in the feces from the orally administered dose.

An attempt was made to evaluate the importance of various factors on absorption of iron in patients having sprue (Table 2). The amount of iron absorbed appeared to be independent of the duration or the activity of the disease as determined clinically. No correlation with excess fecal fat in these patients could be found; this is in agreement with the report of Badenoch and Callender (1).

Relationship of Absorption of Iron to Hemoglobin Content. The patients with sprue were divided into two groups: The first group of patients included those with a hemoglobin content of 12 gm per 100 ml of blood or less. The ranges of radioiron absorbed, expressed as per cent of the oral dose, was 5 to 35 per cent. The mean absorption was 23.7 per cent with a standard deviation (S.D.) of 8.7. In the group of patients in whom the hemoglobin content was greater than 12 gm, the mean absorption of iron was 11.6 per cent with a range of 1 to 24 per cent (S.D. 8.1).

Relationship of Absorption of Iron to Iron in Serum. The same group of patients was again divided into two groups: those with hypoferremia, that is, concentrations of iron of less than 50 micrograms per 100 ml of serum, and those with normal amounts of iron in the serum, that is, 50 to 150 micrograms per 100 ml (Table 4). Again the mean difference between the two groups was found to be statistically significant.

These observations suggest that the patient with nontropical sprue, like the normal person, is able to respond to the stimulus of hypochromic anemia and to hypoferremia by increased absorption of iron from the gastrointestinal tract. However, the response in the patients was limited and insufficient to correct

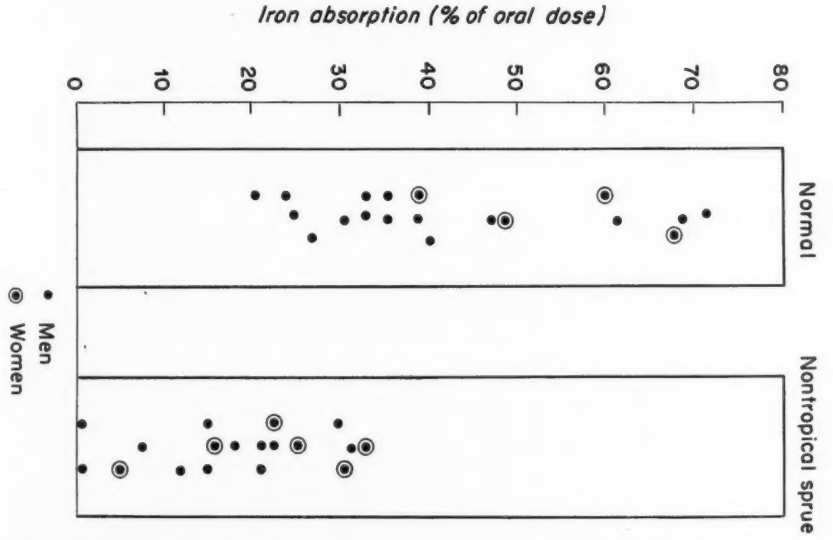

Fig. 1. Iron absorption by 19 normal persons and 17 patients with nontropical sprue. The test was repeated in one patient with sprue.

TABLE 2.
CLINICAL AND LABORATORY DATA IN 17 PATIENTS WITH NONTROPICAL SPRUE

Age, years	*Duration of disease, yr.*	*Clinical activity*	*Blood smear*	*Erythrocytes, million/1 cu mm*	*Hemoglobin, grams/100 ml*	*Serum carotene, I.U./100 ml*	*Fecal fat, grams/24 hr.*	*Serum iron, micrograms/100 ml*	*Per cent of iron absorbed*
Women:									
48	20+	Quiescent	Hypochromasia	4.64	9.6	0	7	25	5
58	4	Exacerbation	Hypochromasia, macrocytes	—	11.1	40	16	33	16
44	16	Quiescent	Scattered macrocytes	—	13.4	60	25	37	24
30	3 Anemia since childhood	Exacerbation	Hypochromasia	3.82	8.8	55	17	20	25
48	8+	Quiescent	Hypochromasia	4.80	11.4	3	20	33	30
34	7+	Exacerbation	Hypochromasia, macrocytosis	3.76	8.0	22	26	18	31
35	2½	Quiescent	Hypochromasia	4.11	8.8	51	19	20	35

Men:									
34	4	Quiescent	Normochromasia, normocytes	5.15	14.6	55	8	68	1
45	9+	Quiescent	Scattered macrocytes	5.19	16.7	60	15	112	1
31	5	Quiescent	Normochromasia, normocytes	5.64	16.6	51	23	133	7
47	43	Exacerbation	—	4.20	15.5	2	58	84	12
54	1	Exacerbation	Not diagnostic	4.47	12.4	3	57	72	15
37	Since child-hood	Exacerbation	Not diagnostic	4.75	13.5	35	26	93	15
43	23+	Quiescent	Hypochromasia	5.75	14.8	24	—	103	18
29	11	Quiescent	Hypochromasia	4.69	12.0	6	26	42	21
47 46	5+ 4+	Quiescent	Normochromasia, normocytes	4.23	12.0	22	15	37	21 23
53	Since child-hood	Exacerbation	Hypochromasia, macrocytosis	4.80	11.6	1	54.6	35	30

an existing anemia owing to iron deficiency. Although one may question the validity of extrapolating from the absorption of 50 micrograms of iron to the absorption of iron in foods or in therapeutic doses, the failure of patients with hypochromic anemia accompanying steatorrhea to respond to oral doses of iron (7-9) supports this observation.

Clearance and Turnover of Radioiron in Plasma. The plasmatic clearance rate and the turnover rate of radioiron in six patients with nontropical sprue are shown in Table 5. The clearance rate is expressed as "T½" or the time required for half of the injected radioiron to be cleared from the plasma. Presumably, this is also the time required for half of the stable iron in the plasma to be turned over. In all patients, "T½" was 72 minutes or less. The iron turnover rate is expressed as milligrams per kilogram of body weight per day and is compared wtih reported normal values (10, 11). Only two of the six patients had normal turnover of plasma iron.

Utilization of Intravenously Administered Radioiron. Radioactive ferrous citrate was given intravenously in single doses which provided 2 to 6 micrograms of the metal to six patients with nontropical sprue. The rate and extent of iron utilization are illustrated in Figure 2, and the hematologic data are recorded

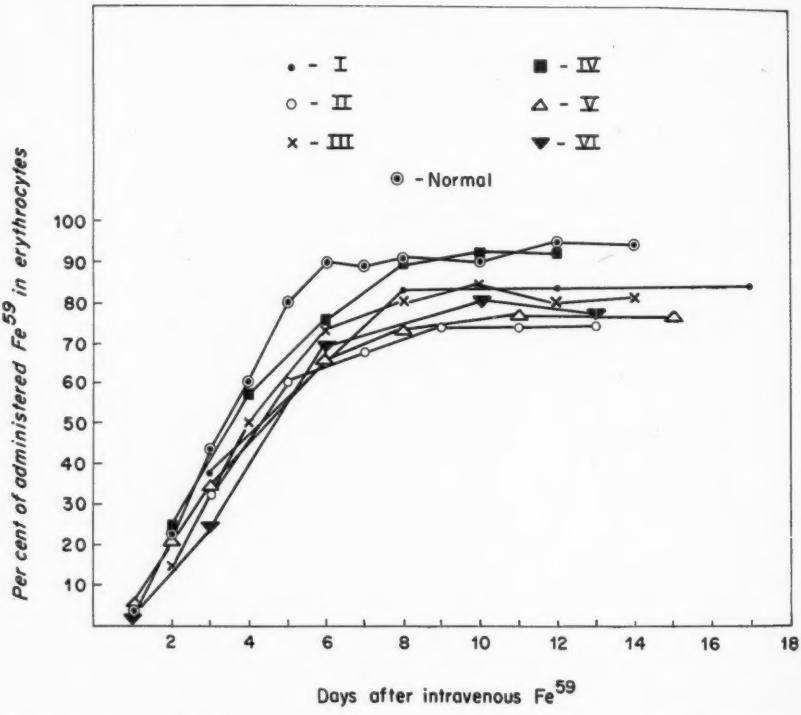

Fig. 2. Incorporation of intravenously injected radioiron into circulating erythrocytes in six patients with nontropical sprue.

in Table 6. Normally 85 per cent or more of injected radioiron is incorporated in circulating erythrocytes (12-14). Of the six patients studied, only one incorporated as much as 85 per cent. This modest decrease in utilization of iron by the erythropoietic tissue of the marrow was present despite the stimulus of iron-deficiency anemia in three patients. Our finding of decreased utilization of injected radioiron is in contrast to normal values reported by Badenoch and Callender (1). The difference may be related to the fact that in their series the blood volume was assumed to be 80 ml per kilogram of body weight, a higher value than we found when the blood volumes were determined by means of radiochromium-labeled erythrocytes.

Survival of Erythrocytes. Survival studies of circulating erythrocytes using radiochromium were performed in six patients having nontropical sprue. The results are expressed as per cent of fall of radiochromium per day. In the clinic laboratories, 2.5 per cent per day is considered as the upper limit of normal, with most values falling between 1.5 and 2.0 per cent per day. It is apparent from Figure 3 that the survival time of erythrocytes was normal.

Gastrointestinal Loss of Blood. In the six patients with sprue studied by means of radioiron and radiochromium given intravenously, stools were collected throughout the period of study and assayed for radioactivity; the radiations from the two isotopes were discriminated and the amount of blood lost in the feces was estimated independently using both isotopes. In two patients, a significant amount of bleeding (more than 5 ml per day by the radiochromium method) (15) was encountered.

The blood loss in the first patient studied is illustrated in Figure 4. A 30 year old woman gave a history of anemia dating back to childhood. She was seen at the clinic on many occasions between 1946 and 1957, during which time

TABLE 3.

RELATIONSHIP OF ABSORPTION OF IRON TO SEX: 19 NORMAL PERSONS COMPARED WITH 17 PATIENTS HAVING NONTROPICAL SPRUE

Diagnosis	*Radioiron absorbed (per cent of oral dose)*	
	Women	*Men*
Normal[8]	36–75 (av. 62)	14–62 (av. 40)
Normal	39–68 (av. 54)	20–72 (av. 39)
Nontropical sprue	5–35 (av. 24)	1–30 (av. 15)

the values for hemoglobin ranged between 8.1 and 11.9 gm per 100 ml of blood. She was treated intermittently with oral doses of iron without significant benefit. In January, 1959, a clinical diagnosis of nontropical sprue was made. The diagnosis was confirmed by laboratory studies, including a jejunal biopsy, which was consistent with the diagnosis of sprue. Because of the unexplained gastrointestinal bleeding, which was demonstrated by the radiochromium method, an exploration was performed to rule out an associated lesion as the cause of her bleeding. Careful search at the time of operation failed to disclose any pathologic condition except for moderately severe mucosal atrophy of the jejunum. Postoperatively, oral doses of iron were tried again without a significant increase in hemoglobin. The patient subsequently received iron intramuscularly with a good hematologic response.

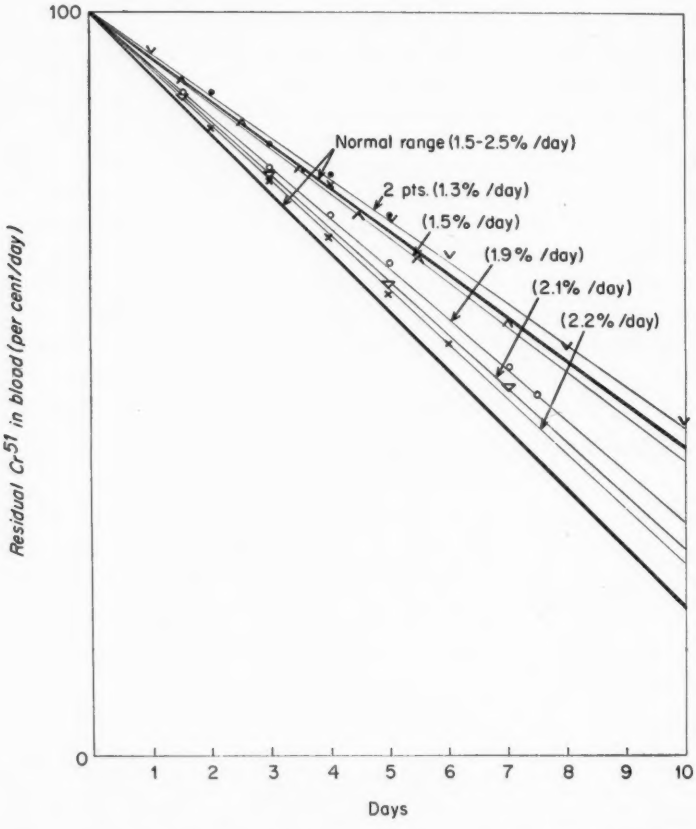

Fig. 3. Disappearance of radiochromium-labeled erythrocytes from the circulation of six patients with nontropical sprue, compared with the normal range. The disappearance in all cases is normal.

The second patient showed a similar blood-loss pattern. Complete investigation failed to reveal any cause for the loss other than the sprue.

A third patient, while under observation, had a sudden drop in concentration of hemoglobin. Specimens of stool gave positive results for occult blood. The only abnormality evident on roentgenograms of the complete gastrointestinal tract was a deficiency pattern of the small bowel. Although this 39 year old woman was still menstruating, gastrointestinal bleeding was presumed to be a factor in the development of hypochromic anemia.

Absorption of Vitamin B_{12}. The Schilling technique (16, 17) for testing absorption of radioactive vitamin B_{12} was performed in eight patients. Commercially available intrinsic factor was used in these studies. The concentrations of hemoglobin in this group ranged from 8 to 16.6 gm per 100 ml of blood. Four patients were anemic. Absorption was normal (more than 8 per cent urinary excretion of the oral dose of radiocobalt in 24 hours) in seven patients. In one patient, absorption was 1 per cent initially and 5 per cent when the test was repeated with an added oral intrinsic factor. This patient's hemoglobin measured 9.6 gm per 100 ml and her blood smear showed moderate hypochromasia without evidence of macrocytosis. The lack of macrocytosis was probably related to the fact that she had been receiving 15 units of liver extract once weekly for several months prior to the study. With the possible exception of this patient, deficiency of vitamin B_{12}, attributable to its malabsorption, did not play an apparent role in the production of anemia in the group studied.

COMMENT

The anemia of nontropical sprue may be normochromic, hypochromic, or macrocytic (with either normoblastic or megaloblastic erythropoiesis (2, 8, 18, 19). This spectrum is not surprising in view of the impairment of absorption of many nutrients essential to normal hematopoiesis.

TABLE 4.

RELATIONSHIP OF ABSORPTION OF IRON TO CONCENTRATION OF IRON IN SERUM IN PATIENTS WITH NONTROPICAL SPRUE

	Iron, micrograms/100 ml serum	
	20-50	*50-150*
Radioiron absorbed, per cent of oral dose	5–35	1–18
Mean	23.7	9.9
S. D.	7.7	6.8

TABLE 5.

RADIOIRON CLEARANCE RATES AND TURNOVER OF IRON IN PLASMA: COMPARISON OF DATA IN SIX PATIENTS WITH NONTROPICAL SPRUE AND REPORTED NORMAL VALUES

Sex and age, years	*Blood smear*	*Hemoglobin, grams/100 ml*	*Serum iron, micrograms/ 100 ml*	*Plasma radioiron clearance, T½ in hours*	*Plasma iron turnover, milligrams/ day*	*Iron turnover, milligrams/kilogram of weight/ day*
Nontropical sprue						
F 30	Hypochromasia	8.8	20	1.00	8.1	0.15
F 24*	Hypochromasia	11.4	23	0.62	13.7	0.24
F 44	Scattered macrocytes	13.4	37	1.20	12.3	0.25

F 48	Hypochromasia	9.6	25	0.43	25.5	0.47
M 53	Hypochromasia, macrocytes	11.6	35	0.93	19.7	0.32
M 47	Normochromasia, normocytosis	12.0	37	0.45	41.2	0.53
Normal persons 5 Persons (10)					20–37 (av. 27)	0.31–0.40 (av. 0.35)
16 Persons (11)						0.4–0.45

*This patient was not included in the absorption study of radioiron.

In some cases of nontropical sprue, it has been suggested (20) that primary malabsorption of dietary vitamin B_{12} may be responsible for the hematologic picture; in others, apparently malabsorption of folic acid or of iron is the more important feature.

In most cases of sprue, however, it is probably defective intestinal absorption of multiple dietary constituents—amino acids, vitamin B_{12}, folic acid, iron, or other substances—which gives rise to the resultant picture in the blood.

Our study emphasizes the importance of defective absorption of iron in nontropical sprue. The mean absorption for normal women was found to be 54 per cent of a 50-microgram dose of iron; none of the seven women with nontropical sprue absorbed more than 35 per cent of this dose. Normal men were found to absorb an average of 40 per cent by this test; none of the men with nontropical sprue absorbed more than 30 per cent.

Whether the malabsorption of iron is due to a primary metabolic defect or whether it is a secondary phenomenon is not known. Badenoch and Callender (1) suggested that it may be due to a deficiency in apoferritin in the intestinal mucosa. Sölvell and associates (7) proposed that mechanical factors, such as edema of the intestinal mucosa, increased mucus, or decreased absorptive area secondary to atrophy of villi, may play a contributory role.

Regardless of the mechanism, it is apparent from the present study that impaired absorption of iron plays a major role in the development of iron-deficiency anemia in patients with nontropical sprue. This inability of the intestinal tract to absorb iron normally persists, whether the patient is in remission or in relapse. In view of this finding there is a potentiality in all patients that iron-deficiency anemia will develop.

In the group of patients with nontropical sprue, which we studied, 10 patients (56 per cent) had anemia. Of this group, 80 per cent had significant hypochromasia of the erythrocytes, a much higher percentage than had been

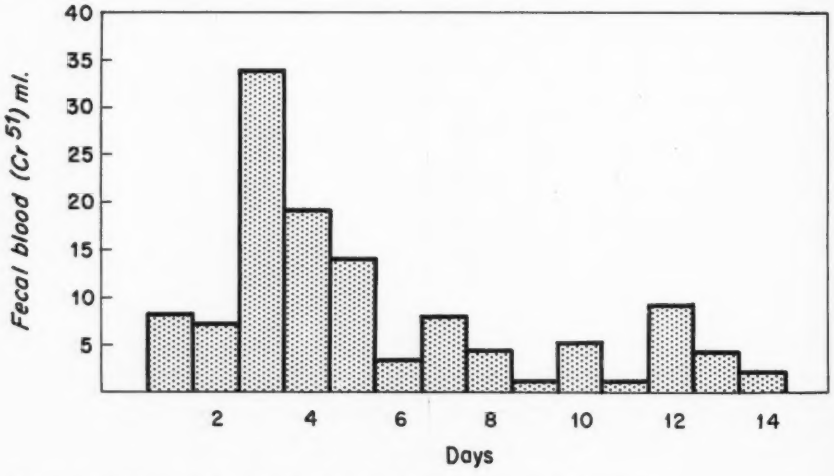

Fig. 4. Gastrointestinal loss of blood in a patient with nontropical sprue.

TABLE 6.

CLINICAL AND SIGNIFICANT HEMATOLOGIC DATA ON PATIENTS WITH NONTROPICAL SPRUE IN WHOM INCORPORATION OF INTRAVENOUSLY INJECTED RADIOIRON INTO CIRCULATING ERYTHROCYTES WAS DETERMINED (FIG. 2)

Case	*Sex and age, years*	*Iron, milligram/100 ml of serum*	*Hemoglobin, grams/100 ml of whole blood*	*Erythrocytes, million/1 cu mm*	*Hematocrit, per cent*	*Blood smear*
1	F 44	37	13.4	—	42	Scattered macrocytes
2	M 47	37	12.0	4.23	40	Normochromasia, normocytosis
3	M 53	35	11.6	4.80	38	Hypochromasia, macrocytosis
4	F 48	25	9.6	4.64	30	Hypochromasia
5	F 24*	23	11.4	4.50	38	Hypochromasia
6	F 30	20	8.8	3.82	29	Hypochromasia

*This patient was not included in the absorption study of radioiron.

reported previously (2, 19). This may be related to treatment because all but one patient with anemia received either liver extract or vitamin B_{12}. In contrast, only one patient with anemia had received iron therapy.

In addition to decreased absorption of iron, some patients are further handicapped by an increased loss of iron secondary to gastrointestinal bleeding, as demonstrated in two of our patients. Although this degree of loss, approximately 1 mg of iron per milliliter of packed erythrocytes, would not be sufficient to produce anemia in a normal person, it could prove significant in a patient who has depleted iron stores and who is unable to compensate normally by increased absorption of iron.

The anemic patient with sprue is unable not only to absorb adequate iron but also to turn over plasma iron at the exaggerated rate usually found in simple iron-deficiency anemia. Further evidence that erythropoietic function is impaired is the incomplete conversion of plasmatic iron to erythrocytic iron.

There was no evidence of any increased loss of iron via the stools other than by bleeding, such as might be attributed to increased secretion of iron, iron loss via the bile, or increased loss secondary to mucosal sloughing. All iron in the feces, excluding that found the first week after injection of radioiron, was iron in hemoglobin as determined by the combined use of radioiron and radiochromium.

Although iron-deficiency anemia does not develop in all patients with sprue, our studies suggest that the patient with nontropical sprue is in precarious iron balance. This is especially true of women who are menstruating. It is suggested that in these patients sudden loss of blood, regardless of etiology, will produce significant anemia. Oral doses of iron would seem inadequate for these patients and therefore parenteral therapy is indicated. Oral doses of iron may be inadequate for a patient having nontropical sprue and iron-deficiency anemia.

SUMMARY

Eighteen patients with nontropical sprue were studied. Impaired absorption of iron was demonstrated in all patients given an oral dose of 50 micrograms of iron labeled with radioiron. Malabsorption of iron seemed to be an important factor in the production of anemia.

Moderately decreased utilization (turnover of iron in the plasma and synthesis of erythrocytes) of iron, studied by means of radioiron, was found in five of six patients.

Survival of erythrocytes was normal in six patients studied wtih radiochromium.

Of eight patients studied with radioactive vitamin B_{12}, only one patient had impaired absorption of this vitamin.

In two patients there was evidence of intermittent, mild gastrointestinal bleeding, measured with radioiron and radiochromium.

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A Theoretical Evaluation of Brain Scanning Systems[1]

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INTRODUCTION

The fact that brain lesions and normal brain tissue tend to take up injected radioactive material to different degrees underlies all attempts to locate brain tumors with gamma ray detectors.

Two fundamentally different collimated scintillation detector systems, responding primarily to photons produced in small diameter cylindrical regions through the head, have been successfully developed for this purpose (Fig. 1). A systematic scan of the head by these detectors produces a two- dimensional mapping of the distribution of radioactivity. The general features of the scanning mechanisms, associated electronic circuitry, displays systems, etc., have been amply described in the literature (1) and will not be discussed here. Rather, a comparison is made of the inherent response characteristics of the two systems.

The positron or "coincidence" system responds primarily to simultaneously detected, oppositely directed, pairs of .511 MEV photons produced by positron annihilation in the cylindrical region (of radius $R_{(coinc.)}$) between the detectors. In addition, a relatively small spurious response is due to the occasional detection of simultaneous, but unrelated, .511 MEV photons from outside this region.

The focusing collimator or "singles" system responds primarily to single photons which come from the region indicated on the right in Fig. 1, the precise shape of which depends on many design parameters. Here we shall deal only with focusing collimators consisting of identical, round, tapered, holes in hexagonal array having a common apex at the focal distance. In such a case, the region of response has a circular cross section of radius R at the focal distance and an hexagonal cross section, somewhat larger, near the collimator. In addition, some gammas from outside this region enter the detector by penetrating the collimator septa.

In order to compare these systems, it has been necessary to develop

1) a criterion based on the statistical nature of count rate information, which depends on both detector sensitivity and the change in count rate over a tumor.

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1. From the Argonne Cancer Research Hospital, operated by The University of Chicago for the United States Atomic Energy Commission, Chicago, Illinois.

2) a theory of detector response to distributed sources, which, for the focusing collimator system, takes into account gamma ray penetration of the septa.

A very significant consequence of the theory of response for focusing collimators is that it allows the design of optimum collimators (most efficient) for a given gamma energy, crystal diameter, collimator material, focal length, radius of resolution and permitted penetration fraction.

The subject involves a great many independent parameters, in illustration of which, systems are compared for a specific set of conditions (crystal size, collimator material, gamma energies, etc.).

An outline of the theory and its implications in medical isotope scanning are presented here.

Criterion for Comparing Systems

Using either system, a tumor is detected by observing a more or less abrupt change in count rate over the tumor region. Since count rate information is subject to statistical variations, it is necessary to scan slowly enough that small changes in count rate can be resolved.

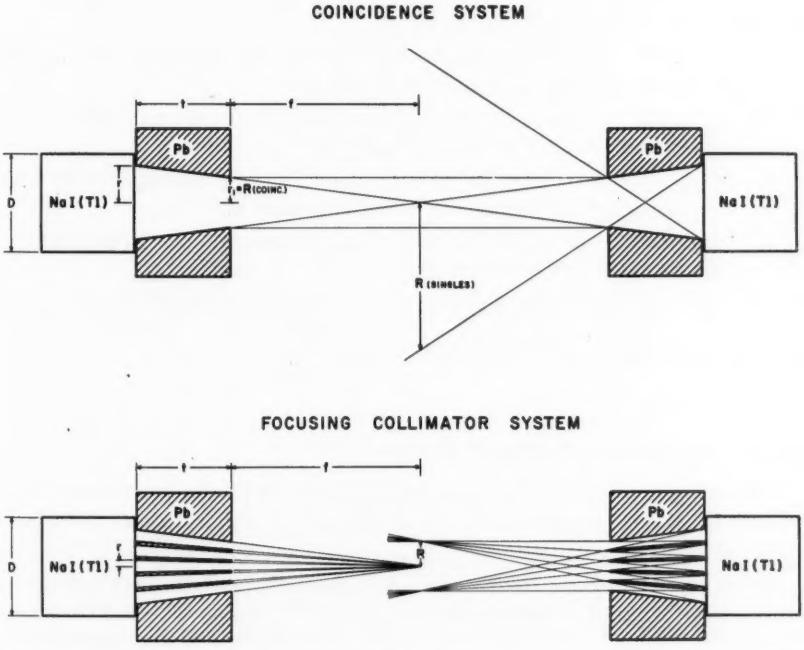

Fig. 1.

If C_o and C_t are the true mean count rates over normal and tumor tissues respectively, then a statistical test of the significance of the difference of observed count rates shows that the time required to detect a tumor is given by

$$\tau = \frac{4Z^2\left(\frac{C_t}{C_o}+1\right)}{C_o\left(\frac{C_t}{C_o}-1\right)^2}$$

where Z is a statistical factor associated with the reliability of tumor detection.

This relation is then used to define the figure of merit of a system, Q, by a function which is inversely proportional to the detection time.

$$\tau = \frac{Z^2}{Q} \text{ or } Q = \frac{C_o\left(\frac{C_t}{C_o}-1\right)^2}{4\left(\frac{C_t}{C_o}+1\right)}$$

Although the figure of merit has been derived from a consideration of detection time, alternative interpretations are possible.

If for the same resolution (R), radiation dosage to the patient, and reliability of tumor detection (Z), the figure of merit Q_A of system A is ten times greater than the figure of merit Q_B of system B then

1) for equal resolution, dosage and reliability, the required scanning time for system A is one-tenth that for system B.

or 2) for equal resolution, dosage and scanning time, system A will be more reliable in detecting tumors than will system B.

or 3) for equal resolution, scanning time, and reliability, the required radiation dosage for system A is one-tenth that for system B.

or 4) for equal dosage, reliability and scanning time, the resolution of system A can be improved over system B.

In order to compute the figure of merit of a system, equations are needed for the normal count rate C_o and contrast ratio, $\frac{C_t}{C_o}$.

Detector Response to Distributed Sources

While a computation of the response of a detector to an arbitrary source distribution is extremely complicated, the response to a uniform sheet distribution can be described very simply.

It has previously been pointed out (2, 3) that, as a uniform sheet distribution of radioactive material is moved along the axis of either a focusing collimator system or a coincidence system, the count rate is constant. This is true provided only that the sheet is large enough to cover the entire region viewed by the collimator

and that a negligible number of gammas penetrates the collimator and surrounding shielding. This has been adequately demonstrated for a coincidence system (2). For a focusing collimator system, measurements made in this laboratory with a large sheet distribution of Hg^{197} show that the count rate is constant $\pm$ 2 per cent to a distance of 25 cm from the collimator.

The significance of this is twofold. 1) It enables us to find uniform sheet distributions which are equivalent (produce the same count rate) to the cylindrical regions through the head "seen" by the detectors. This can be done for both normal and tumor regions. 2) The response of a detector to a sheet distribution is easily computed for a sheet at zero distance; that is, against the face of the collimator.

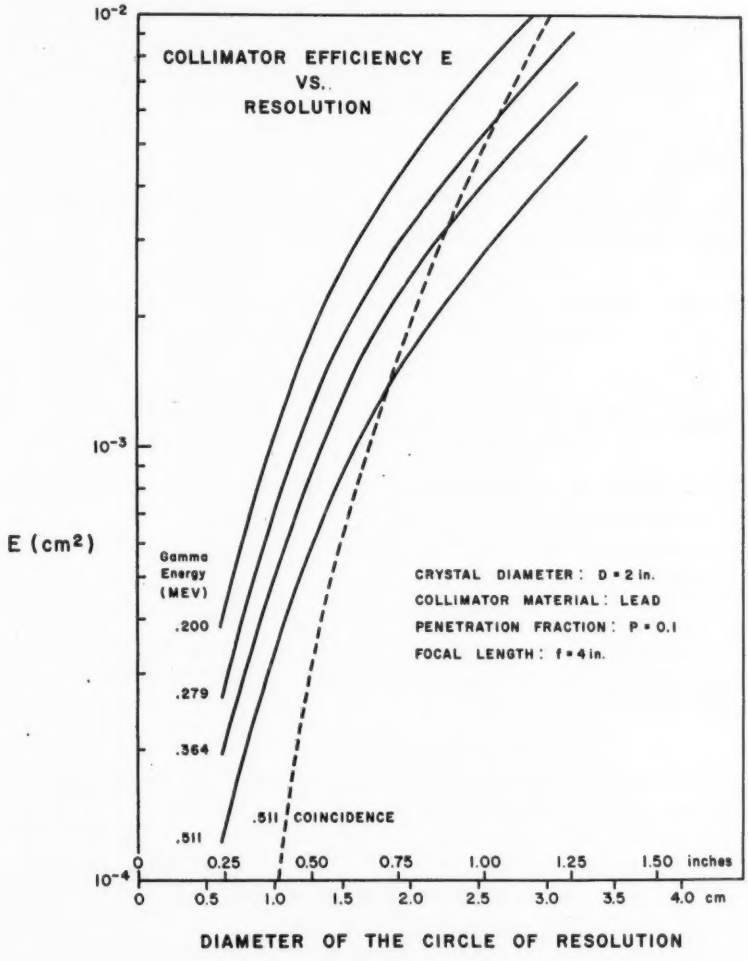

Fig. 2.

For either a focusing collimater or a coincidence system the response to a uniform sheet distribution can be written in the form

$$C = E\,(1+P)\,\eta\sigma$$

where

$C \dfrac{(\text{counts})}{\text{sec}}$ = count rate

$E(\text{cm}^2 =$ geometrical efficiency of the collimator for a sheet distribution

$P =$ penetration fraction (or the efficiency due to penetration, relative to the geometrical efficiency.)

$\eta =$ overall crystal efficiency

$\sigma\left(\dfrac{\text{photons}}{\text{cm}^2\text{-sec}}\right) =$ photon density on the sheet (emanating in all directions.)

Equations for the Detectors

The geometrical efficiency of the collimator for a sheet distribution can be found by integrating over a sheet at zero distance.

$$\text{(F.C.)} \quad E \cong \frac{N\pi R^4}{2\left(8f^2+R^2\right)\left(\frac{R}{r}+2\right)^2}\ (\text{cm}^2) = \frac{N\pi r^4}{2\left(2t^2+r^2\right)\left(1+\frac{t}{f}\right)^2}$$

$$\text{(Coinc.)} \quad E \cong \frac{\pi R^4}{2(8f^2+R^2)}\ (\text{cm}^2)$$

$R =$ radius of the region of view at the focal distance.
$f =$ focal distance.
$N =$ number of holes.
$r =$ base radius of the holes.
$t =$ collimator thickness.

If the source is large enough to cover the entire viewing field of the large hexagonal hole formed by removing all septum material, then the equation for penetration fraction has the form

$$\text{(F.C.)} \quad P = \left[\frac{E_H}{E} - 1\right] \exp\left[-\lambda t\left(1-\frac{b}{b_H}\right)\right], \text{ where}$$

$E_H =$ geometrical efficiency of the large hexagonal hole.
$\lambda =$ attentuation coefficient in collimator material.
$b =$ total base area of the N small holes.
$b_H =$ base area of the large hexagonal hole.

Using for E_H the efficiency of a round tapered hole with equal base area, this equation can be put in a more useful form.

$$\text{(F.C.)}\quad P = \left[\frac{27D^4\left(1+\frac{R^2}{8f^2}\right)}{64\pi^2 r^4 N\left(1+\frac{3\sqrt{3}\,D^2R^2}{64\pi r^2 f^2}\right)} - 1\right] \exp\left[\frac{-2rf\lambda}{R}\left(1-\frac{8N\pi r^2}{3\sqrt{3}\,D^2}\right)\right]$$

D = diagonal of the hexagonal hole, which is usually set equal to the crystal diameter.

λ = attentuation coefficient in collimator material.

(Coinc.) For the coincidence system, it is assumed that the penetration fraction is negligible.

If only "photopeak" pulses are counted, then

(F.C.) $\eta = ip$

(Coinc.) $\eta = (ip)^2$

where η = crystal efficiency for the detector system.

i = interaction ratio.

p = photofraction.

Equations for the Source

Assuming that the concentration of isotope is uniform in normal brain tissue, the activity in a cylinder of normal tissue "seen" by the detectors can be reduced to a sheet distribution which produces the same number of counts.

$$\text{(F.C.)}\quad \sigma_0 = H'\rho = \left[\frac{1-e^{-\mu_0 H}}{\mu_0}\right]\rho$$

$$\text{(Coinc.)}\quad \sigma_0 = H'\rho = He^{-\mu_0 H}\,\rho$$

$\sigma_0\left(\frac{\text{photons}}{\text{cm}^2\text{-sec}}\right)$ = photon density on the equivalent sheet distribution.

$H(\text{cm})$ = thickness of the head.

$H'(\text{cm})$ = equivalent or reduced head thickness when attenuation in the head is taken into account.

$\mu_0(\text{cm}^{-1})$ = attentuation coefficient in brain tissue.

$p\left(\frac{\text{photons produced}}{\text{cm}^3\text{- sec}}\right)$ = photon density in normal tissue.

$$p\left(\frac{\text{photons produced}}{\text{cm}^3\text{-sec}}\right) = 3.7 \times 10^4 \left(\frac{\text{disint.}}{\text{sec-}\mu\text{c}}\right) \times A \left(\frac{\mu\text{c}}{\text{cm}^3}\right) \times n \left(\frac{\text{photons}}{\text{disint.}}\right)$$

If the concentration of isotope in the tumor is uniform and the tumor is uniformly thick and large enough to cover the cylindrical region of view of the detectors, then the equivalent sheet distribution is given by

$$(\text{F.C.})\quad \sigma_t = \left[H' + (U-1)\, e^{-\mu_0 d_1} \left(\frac{1 - e^{-\mu_0 | d_2 - d_1 |}}{\mu_0} \right) \right] \rho$$

$$(\text{Coinc.})\quad \sigma_t = \left[H' + (U-1)\, | d_2 - d_1 |\; e^{-\mu_0 H} \right] \rho$$

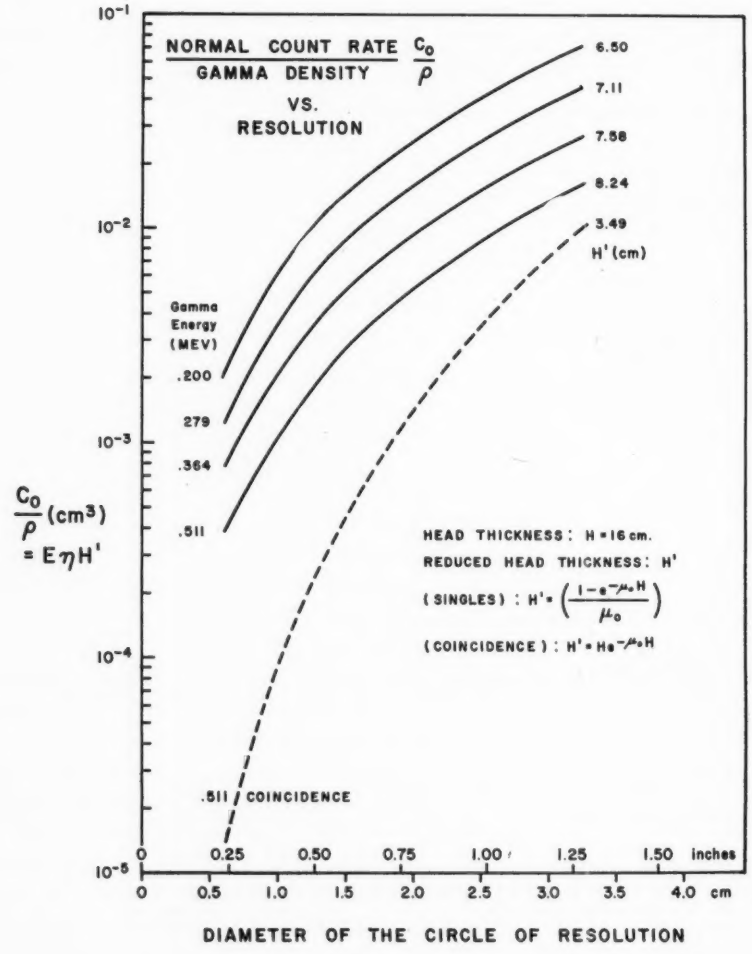

Fig. 3.

$\sigma_t\left(\frac{\text{photons}}{\text{cm}^2\text{-sec}}\right)$ = photon density on the equivalent sheet distribution.

U = uptake ratio, or the concentration of isotope in tumor tissue relative to normal tissue.

d_1 = depth to the surface of the tumor.

$|d_2 - d_1|$ = tumor thickness in the direction of the detector axis.

Since the normal and tumor count rates are proportional to σ_o and σ_t respectively, the intrinsic contrast ratio is given by $\frac{\sigma_t}{\sigma_o}$.

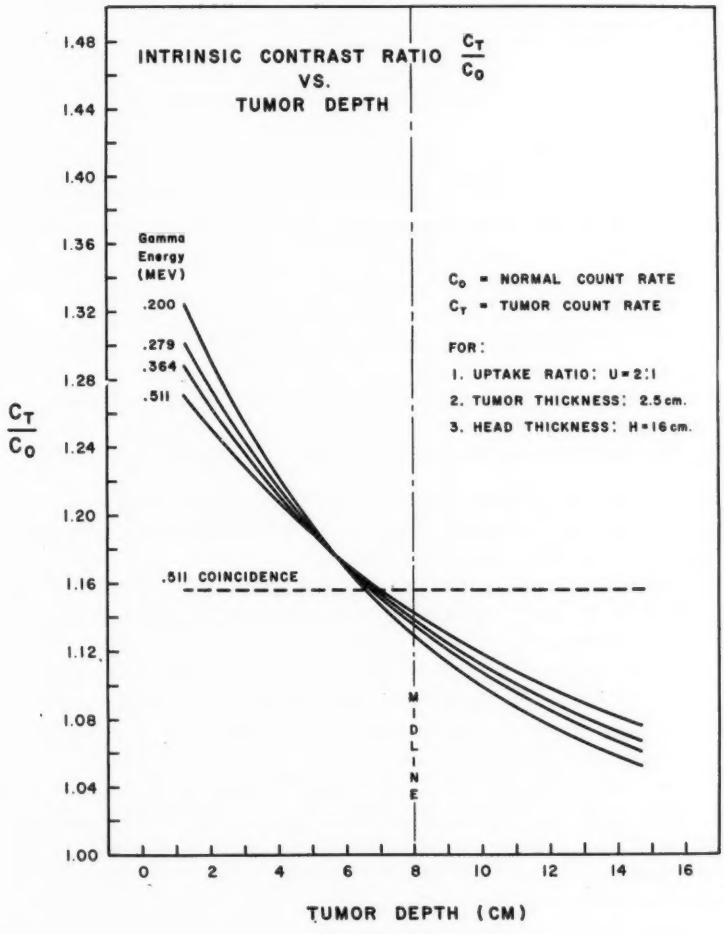

Fig. 4.

$$(F.C.)\ \frac{C_t}{C_o} = \frac{\sigma_t}{\sigma_o} = 1 + (U-1)\left[\frac{1 - e^{-\mu_o |d_2 - d_1|}}{1 - e^{-\mu_o H}}\right] e^{-\mu_o d_1}$$

$$(Coinc.)\ \frac{C_t}{C_o} = \frac{\sigma_t}{\sigma_o} = 1 + (U-1)\frac{|d_2 - d_1|}{H}$$

Figure of Merit Q

The figure of merit of a system can then be computed for any system and tumor by first computing C_o and $\frac{C_t}{C_o}$.

$$Q = \frac{C_o \left(\frac{C_t}{C_o} - 1\right)^2}{4\left(\frac{C_t}{C_o} + 1\right)}$$

As an illustration of the theory, a comparison is made between coincidence systems and focusing collimator systèms designed for four gamma energies.

For this comparison, we have arbitrarily chosen the following conditions.

1) 2″ x 2″ NaI(T_1) crystals (D = 2)
2) LEAD, for the collimator material (λ)
3) MIDLINE OF THE HEAD, for the focal distance (f = 4″)
4) 0.1, for the permitted penetration fraction (P = .1 is considered negligible)
5) .511 MEV, .364 MEV, .279 MEV, .200 MEV for the focusing collimator systems.
6) .25″ to 1.25″ for the range of diameter of the circle of resolution (2R).

The problem of optimum focusing collimator design then reduces to the problem of finding the hexagonal array (characterized by values of N and r) for which the collimator efficiency (E) is maximum.

A procedure has been carried out on UNIVAC for some 300 combinations of values of D, f, R, P, λ (4), yielding, for each combination, the values of N and r for which E is maximum

For the specific conditions listed above, the results of these computations are shown in Fig. 2, where optimum collimator efficiency is plotted against resolution for each gamma energy. The geometrical efficiency of a coincidence system with f = 4″ is also shown (dashed line).

In order to minimize the effects of scattered radiation, it has been assumed that only "photopeak" pulses are counted. Using interpolated values from published tables (5) of interaction ratio and photo fraction, the crystal efficiency has been computed for each system. Weighting the curves of Fig. 2 by crystal efficiency gives detector efficiency, $E\eta$.

The count rate over normal tissue ($C_o = E\eta\ \sigma_o$) may then be determined if, for equal radiation dosages, the concentration of isotope in normal tissue is spe-

cified for each system. Since a degree of arbitrariness is involved in computing concentrations of different isotopes which produce equal radiation dosages, this aspect of the problem is not dealt with here. Instead, the comparison is based on the assumption that equal numbers of photons are produced/cm³-sec (equal p's), for all systems.

It is possible, however, to take the discussion one step further. Making allowance for the reduction in count rate due to attenuation in the head, a factor which is proportional to the count rate over normal tissue ($\frac{C_o}{p} = E\eta H'$) is plotted against resolution in Fig. 3.

In Fig. 4, the intrinsic contrast ratio is plotted against tumor depth for a relatively large tumor, 2.5 cm thick, having an uptake ratio of 2:1. Assuming that the tumor diameter is at least equal to its thickness, the intrinsic contrast

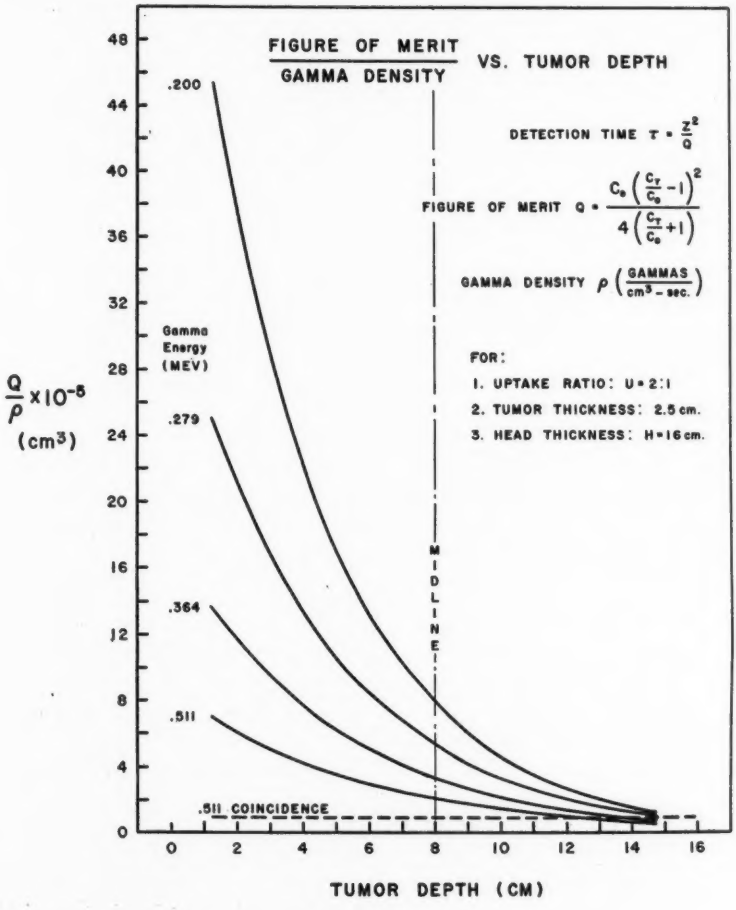

Fig. 5.

ratio is observed at the midline (f) provided that 2R $\leqq$ tumor diameter. This ratio is observed at other tumor depths only if the tumor covers the region of view, which may be larger.

For each system, a factor $\frac{C_o}{\rho}$ (for 2R = 2.5 cm) can be selected from Fig. 3, and combined with corresponding values of $\frac{C_t}{C_o}$ from Fig. 4 to determine the normalized figure of merit $\frac{Q}{\rho}$. This is plotted against depth to the center of the tumor in Fig. 5. For a midline tumor, the figure of merit of a focusing collimator system designed for .511 MEV, relative to that of a coincidence system with the same resolution, is 2:1. A similar calculation for a 1 cm midline tumor shows this ratio to be 10:1 (when 2R = 1 cm for both systems).

Experimental confirmation of the theory will be presented in a future paper.

CONCLUSIONS

Under the conditions listed for the illustration, it appears that focusing collimator systems can be designed for .511 MEV radiation which are superior to coincidence systems by factors of 2 to 10 (depending on resolution) for midline tumors. These factors increase for tumors not on the midline.

Making the further assumption of equal numbers of photons produced/cm^3-sec for all systems, the figure of merit for focusing collimator systems increases with decreasing gamma energy down to .200 MEV, the low energy limit of this investigation. It can be generally concluded therefore that the advantages of low energy gamma radiation for brain scanning have not yet been fully exploited.

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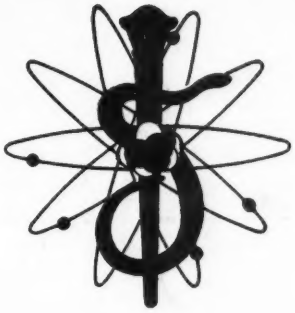

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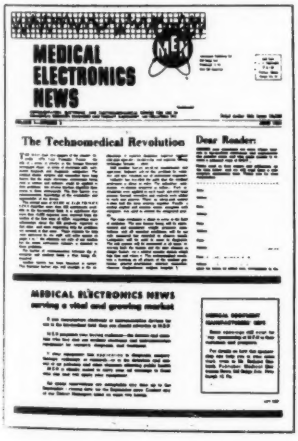
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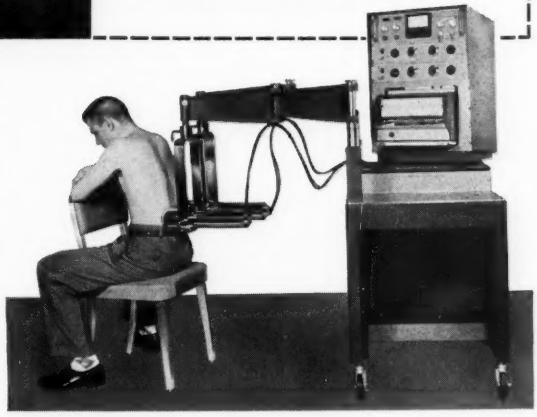

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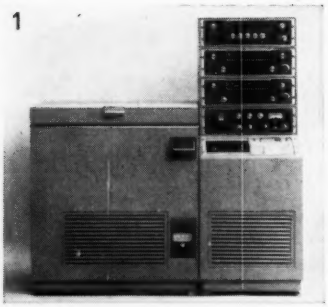

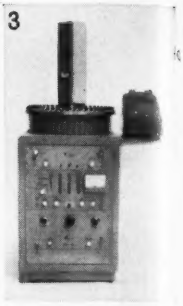

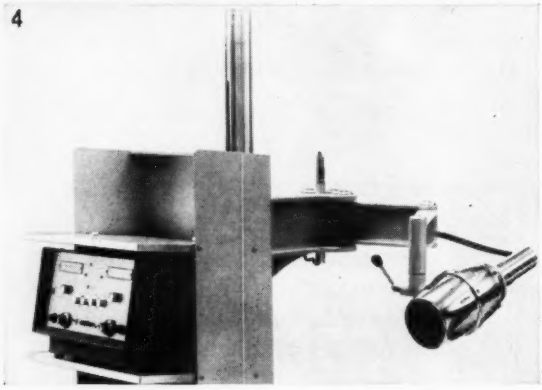

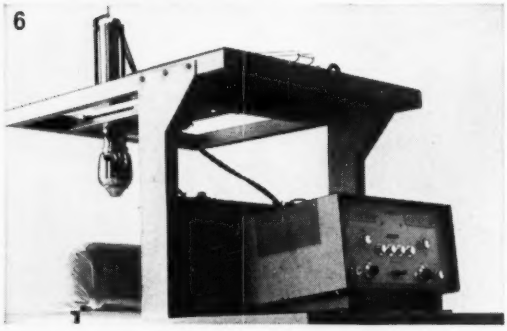

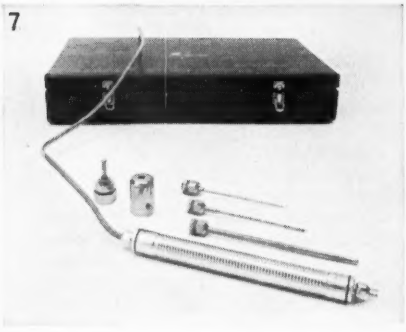

1. Automatic, temperature-controlled liquid scintillation counting system Model 703 shown with two scalers, timers and digital recorder. For counting large numbers of carbon-14 and tritium samples with highest efficiency and precision.

2. Scintillation well detector Model DS-303 and spectrometer Model 132B for measurement of radioactivity in urine, blood and plasma.

3. Automatic system for analysis of gamma samples employs Model C120 sample changer with shielded well scintillation detector plus printing timer, scaler and spectrometer.

4. Probe scintillation detector with three-inch crystal and scaler-spectrometer shown mounted on Model 1710 clinical stand constitute instrumentation for thyroid uptake measurements.

5. Versatile system for in vivo procedures. Clinical stand supports as many as three scintillation detectors together with associated equipment such as ratemeters, recorders, and a scaler-spectrometer for evaluation of thyroid and kidney function and estimation of cardiac output and myocardial blood flow.

6. Model 1700A isotope scanner produces graphic record of radioisotope distribution in body area 14 x 17 inches. Used with collimated scintillation detector.

7. Model DS8-1 light-weight needle-probe scintillation detector set is furnished with four probes. Used with scalers, ratemeters or gamma spectrometer systems to localize radioisotope concentrations in tissue during surgery.

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The seven photographs at the left portray a key resource of the medical and scientific community. They are representative of more than 200 instruments and systems designed by Nuclear-Chicago for biomedical research and diagnostic medicine. This comprehensive line offers a growing body of isotope users proved reliability together with precise, reproducible performance. Wide acceptance is the result.

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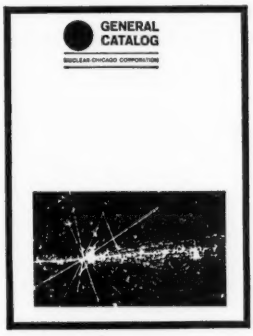

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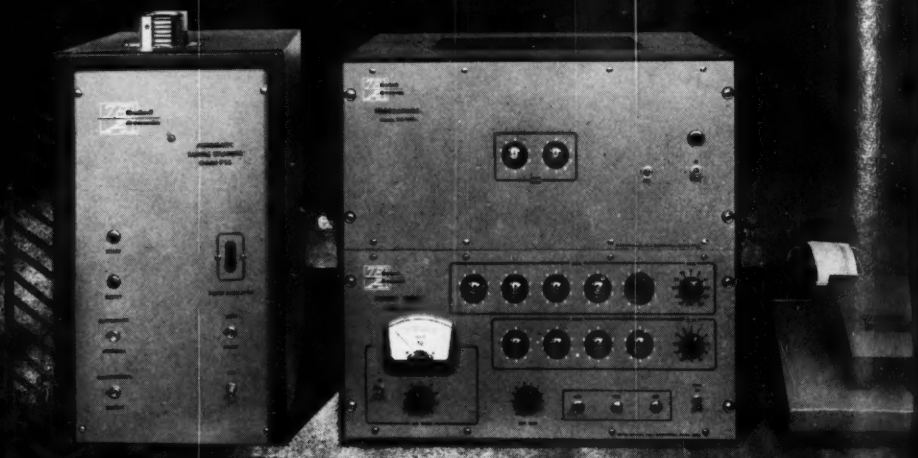

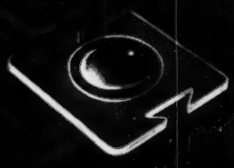

This simplified system incorporates the latest techniques and instrumentation for automatic detection, timing, counting and data presentation. It accommodates up to 35 samples, processes and records results including sample number, time, count and, on request, count rate. The overriding time and count functions are performed by the new B/A Model 135 Scaler-Timer.

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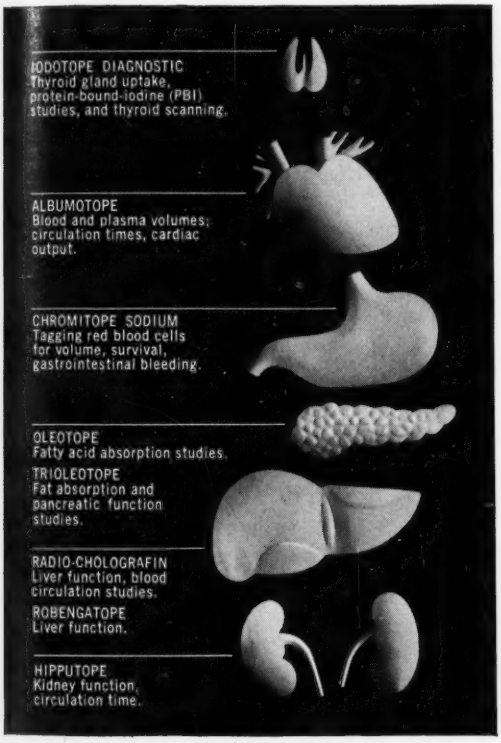

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Cancer Research

"Conceptual Advances in Immunology and Oncology" will be the subject of the Sixteenth Annual Symposium on Fundamental Cancer Research, to be held March 1, 2 and 3, 1962, at The University of Texas M. D. Anderson Hospital and Tumor Institute, announced Dr. Felix L. Haas, chairman of the symposium committee.

The three-day program will be divided into morning sessions from 9:00 A. M. to 12:00 Noon and afternoon sessions from 3:00 P. M. to 6:00 P. M. Titles of the sessions are: "Theories of Antibody Production", "Metabolic Control of Antibody Synthesis", "Genetic Basis of Immune Response", "The Nature of the Antigen-Antibody Reaction", "Transplantation and Immunological Tolerance" and "Cancer Specific Antigens".

An annual event at the symposium is the presentation of the Bertner Foundation Award. The Award was established in 1950 to honor the late Dr. E. W. Bertner, first acting director of M. D. Anderson Hospital and Tumor Institute, and is awarded for outstanding contribution to some field of cancer research.

Further information on the meeting may be obtained from the Publications Department, The University of Texas M. D. Anderson Hospital and Tumor Institute, Texas Medical Center, Houston 25, Texas.

The Second International Congress of Radiation Research will be held in Harrogate, England, August 6-11, 1962. The Congress will be concerned with research into the physical, chemical, and biological effects of ionizing radiation. The Radiation Research Society, in cooperation with the National Academy of Sciences-National Research Council, is exploring possibilities for providing partial travel support to qualified participants. Applications must be submitted prior to February 1, 1962. Forms for this purpose are available from the Committee on Travel Grants, Room 319, 2101 Constitution Avenue, N.W., Washington, 25, D. C. Further information about the Congress may be obtained from the Secrtary-General, Dr. Alma Howard, Mount Vernon Hospital, Northwood, Middlesex, England.

Announcement to Authors
Preliminary Notes

Commencing with the October, 1961 issue, space will be reserved in each issue of THE JOURNAL OF NUCLEAR MEDICINE for the publication of one preliminary note concerning new original work that is an important contribution in Nuclear Medicine.

Selection of the preliminary note shall be on a competitive basis for each issue. One will be selected after careful screening and review by the Editors. Those not selected will be returned immediately to the authors without criticism. Authors may resubmit a rejected or revised preliminary note for consideration for publication in a later issue. The subject material of all rejected manuscripts will be considered confidential.

The text of the manuscript should not exceed 1200 words. Either two illustrations, two tables, or one illustration and one table will be permitted. An additional 400 words of text may be substituted if no tables or illustrations are required. Only the minimum number of references should be cited.

Manuscripts should be mailed to the Editor, Dr. George E. Thoma, St. Louis University Hospital, 1325 South Grand Blvd., St. Louis 4, Missouri. They must be received before the first day of the month preceding the publication month of the next issue, e.g., preliminary notes to be considered for the January issue must be in the hands of the Editor before December 1.

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SEAT BELTS, if used in every car, could save at least 5,000 lives a year . . . reduce injuries by one-third, according to the National Safety Council. Many of those saved from injury or death would be youngsters—for *drivers kill and cripple more children* than any disease. Protect *your* children . . . drive with loving care. Give them the security of seat belts.

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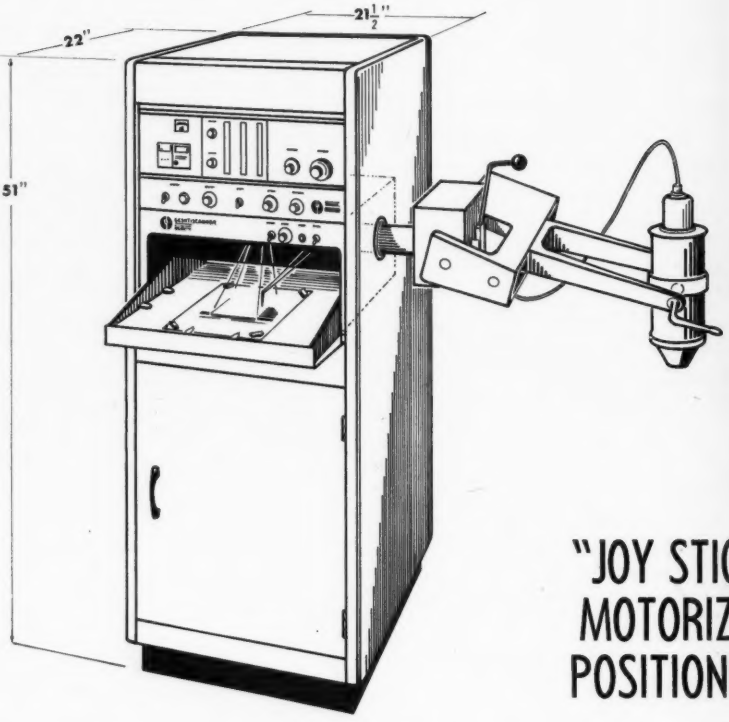

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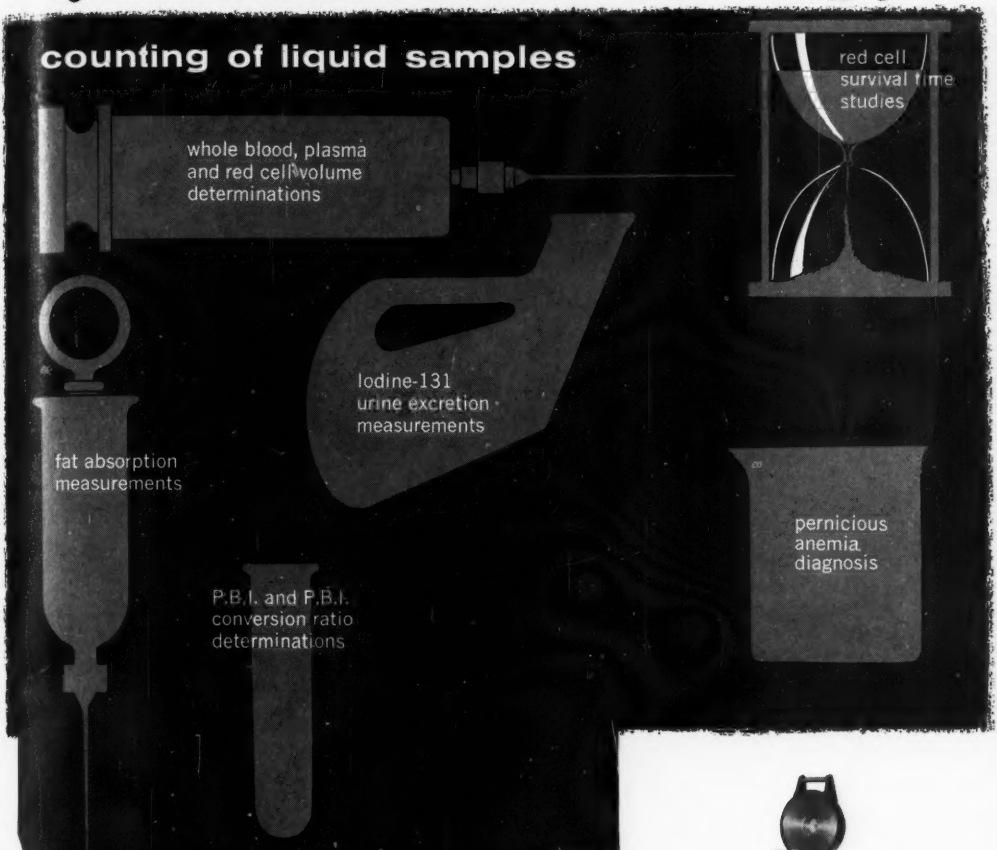
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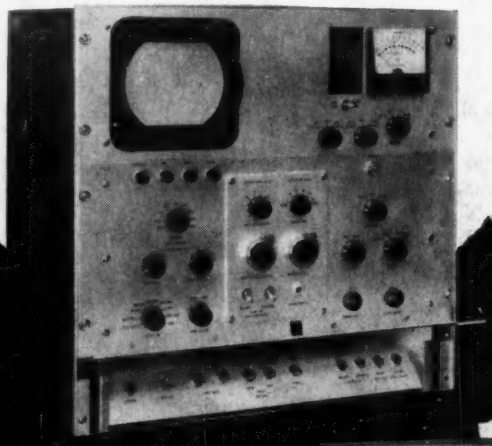

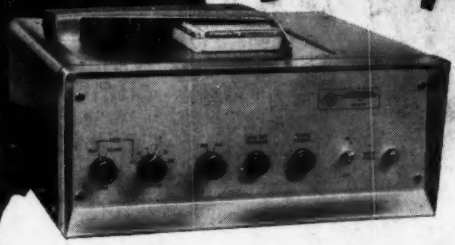

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